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(54) Title: HIGH-PRECISION COMPUTER-AIDED MICROSCOPE SYSTEM

(57) Abstract: A microscope frame structure having a front brace for added stability and having a dual plate structure. The front brace is rigidly coupled to the front ends of an upper portion and a base portion. The upper portion then carries optical elements such as a camera for instance. In effect, the optical elements thus reside on a bridge structure, with substantially the same structural support at both ends of the bridge. The arrangement is particularly useful in automated specimen imaging and analysis systems. The dual frame is composed of an upper plate, which supports a sample, a lower plate which contacts an elevating screw, and a spacer post in between the upper plate and lower plate. This configuration allows for more stable movement of samples.

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HIGH-PRECISION COMPUTER-AIDED MICROSCOPE SYSTEM

REFERENCE TO RELATED APPLICATIONS

This application claims priority to U.S. Patent Application Serial No. 09/439,150, filed November 12, 1999. This application incorporates by reference in its entirety U.S. Patent Application Serial No. 09/439,150, filed November 12, 1999.

BACKGROUND OF THE INVENTION

1. Field of the Invention

The present invention is related generally to the field of microscopy, and more particularly to the configuration of optical microscopes and microscope-based electronic imaging systems.

2. Description of the Related Art

In its most basic form, a microscope typically includes a base, a plate or stage for holding a sample, a magnifier commonly including a series of lenses, and a viewer for presenting a magnified image to an observer. The principal purpose of a microscope is to create a magnified image of a sample of a specimen and to accurately present the enlarged image to an observer or to an electronic imaging apparatus used for image acquisition, display, measurement, analysis, communication, archiving, or data management.

Over the years, microscopes have evolved into very complex and sophisticated optical instruments, taking a variety of forms. While most microscopes are manually operable and may present a magnified image for viewing by an operator, one of the most important recent advances in microscopy has been the development of automated, computer-aided microscopes. Most computer-aided microscopes include the conventional elements of manually operated microscopes but are further configured in combination with a digital computer. The computer may serve a variety of functions, such as, for instance, controlling the position of a motorized stage, controlling the focusing system, or controlling other optical components such as microscope objectives.

In a typical arrangement, a computer-aided microscope system includes an electronic photodetector or imaging system such as a video or CCD camera interconnected to the

viewer, with the output from the detector being fed into a computer processor for a variety of functions including analysis or image enhancement or display. The computer processor in turn may provide control signals to the microscope, for instance, to control the stage position, focus drive or other aspects of the system. Provided with this arrangement, a computer-aided microscope may enable the automatic analysis of a wide variety of objects, such as cytological samples, pathology specimens or semiconductor chips (solid state devices). Further, the automated analysis may be easily enhanced by appropriate computer programming as well as by the addition of assorted peripherals (such as data storage devices and interactive user-input devices).

In automated cytology sample analyses, for instance, a specimen is drawn from a patient, a sample is prepared from that specimen, and the sample is placed into the automated microscope. An image detector (e.g., CCD camera) may electronically scan the sample and thereby receive digital images of discrete regions of the sample. The detector may then feed these digital images to a processor, which stores the images in memory and analyzes the images. In addition, the processor may receive from the microscope an indication of the spatial coordinates of the stage (e.g., X and Y planar coordinates, and a Z focus coordinate). Through complex image analysis algorithms, the processor may identify cellular matter of interest in the sample and may then mark in memory an indication of the stage position coordinates associated with that cellular matter. Samples may be deposited on slides with fiducial marks to ensure that the X-Y locations are accurate from microscope to microscope or calibration procedures can be developed and used to ensure that the X-Y coordinates apply from machine to machine.

In turn, once the processor completes its analysis, it may generate a routing function keyed to the stage coordinates and defining an order by which the automated microscope should present areas of the sample to an operator such as a cytotechnologist. Through use of this routing function, the computer processor may thus control the microscope stage position and microscope focus, and may thereby present the cellular matter or other objects or optical fields of interest to the operator through the microscope field of view. In addition, or alternatively, the automated-microscope system may be configured to include a computer monitor, which may present the microscopic fields of view to the operator without requiring the operator to look through the microscope ocular(s).

As a general rule, precision, accuracy and speed are critical to the useful operation of a microscope in addition to the quality (e.g., resolution) of the optical magnification devices

and processes. This is particularly important for computer-aided microscopy systems. In cytological specimen analysis, for instance, a cytotechnologist typically needs to be able to locate atypical or abnormal cells in specimens rapidly, precisely and accurately, since cells are typically less than a few hundred microns in their maximum linear dimension. While many cancer-related cytological changes are characteristic and can be detected and classified with a high degree of accuracy by an appropriately configured microscope, inaccurate or imprecise microscope configurations can be the source of unacceptable false positive or false negative cell classifications and sample specimen diagnoses.

Further, modern vision systems employing computer-aided image analysis have imposed on microscopes even more stringent requirements for high precision, mechanical stability and optical and illumination repeatability. Unfortunately, however, traditional mechanical (*e.g.*, fully manual) microscope systems, as well as many of the currently available automated microscope systems, have not provided the positional accuracy, repeatability, stability and resolution required for reliable, reproducible quantitative microscopic imaging applications.

To ensure proper operation, for instance, a microscope must be as stable as possible. The microscope must be stable in the presence of ambient vibrations and also stable with respect to internally introduced vibrations. However, the motorized stages in some existing automated-microscope configurations are unstable. Consequently, these existing systems cannot rapidly, accurately, precisely and repeatedly locate and focus on diagnostically significant areas of a sample from a specimen.

Traditional optical microscopes, for example, enable movement of the stage by way of a cantilevered system that is offset from the optical path of the microscope. In other systems, as the present inventors have recognized, the stage is moved through the exertion of a force at a position other than the center of gravity or center of effort of the plate. Consequently, existing microscopes tend to generate yaw, pitch, roll and droop errors (*i.e.*, introduce a third derivative, "jerk") during stage movement. These errors are particularly troublesome in the context of automated computer-aided microscopy. It is also problematic for human observers who also need stage motion to be dampened before they can visualize a temporally stable image.

Similarly, in microscope systems that employs a detector (such as a camera) to capture magnified images, the detector itself must remain stable during operation. However, in most such systems, the detector is attached only to the viewer of the microscope. As

recognized by the present inventors, this configuration thereby increases the likelihood that the camera will become unstable or misaligned during operation, potentially rendering the camera unable to capture magnified images properly.

Further, to ensure proper operation, the sample being analyzed in a microscope needs to be properly illuminated and have proper spectral density. This is particularly the case in microscopes that employ detectors, such as cameras, to capture magnified images, as the detectors are often configured to operate optimally with a particular level of light. This is also the case whenever there is spectral-based analysis of a sample. In these systems, if the sample is illuminated with insufficient or excessive light, or with improper spectral characteristics, the detector may need to compensate for the imperfect illumination and thereby operate less than optimally. Still further, the level of illumination in a microscope is important even for manual viewing through the oculars, as appropriate illumination is required to allow human perception of the magnified sample through the microscope lenses.

Additionally, a typical microscope includes a variety of adjustable elements. These elements include, for instance, condenser lens focus, condenser lens centration, lamp filament centration, condenser aperture, and field diaphragm. To ensure proper operation of the microscope system, most or all of these elements need to be adjusted by an operator or an automated controller before analysis can begin. For example, to properly focus a diffused image at the light source, the condenser lens focus must be properly adjusted. As another example, to achieve lamp photon emitter centration, an operator must typically adjust the microscope light source if the light source is not properly centered. Unfortunately, however, adjustment of these elements can be time consuming and tedious.

In view of the deficiencies in the art, there is a need for an improved configuration of a high-precision, automated or computer-aided microscope.

SUMMARY OF THE INVENTION

An exemplary embodiment of the present invention provides an improved microscope system. In one aspect, the system includes an improved method and apparatus for guiding the plate. In a second aspect, the system includes an improved method and apparatus for moving the stage. In a third aspect, the system includes an improved method and apparatus for maintaining proper illumination. In a fourth aspect, the system includes an improved method and apparatus for maintaining proper spectral density. In a fifth aspect, the system includes an improved method and apparatus for maintaining proper placement of the light source, for configuring a fixed optics system. In a sixth aspect, the system includes an improved method and apparatus for maintaining proper placement of the imaging system. In a seventh aspect, the system includes an improved method and apparatus for fixing the optics in the microscope for an automated system. In an eighth aspect, the system includes an improved method and apparatus for increasing the stability of the microscope during movement.

The invention may facilitate enhanced electronic image capture and analysis and may be particularly suitable for use in the context of cytological or histological sample analysis. However, the invention is not limited to analysis of biomedical specimens but may more generally be used for analysis of any type of sample.

A principal object of the present invention is to provide a computer-aided microscope system that facilitates quick, stable and reproducible microscopic presentation of goals. Another objective of the invention is to provide a microscope having geometric accuracy in the three-motion axes. Still another object of the invention is to provide a microscope that remains stable when performing high-speed moves.

A further object of the invention is to provide a microscope that does not vary appreciably in terms of optical alignment. Yet a further objective of the invention is to provide a microscope that has constantly controlled and repeatable illumination systems. Still another object of the invention is to provide a microscope that may be incorporated into higher level imaging and analytical instruments. Yet another object of the invention is to provide a microscope in combination with a detector, such as a camera or a photomultiplier tube assembly, whereby the photodetector(s) remain(s) in proper alignment during their image acquisition operation.

These and other features and advantages of the present invention will be better understood by reading the following detailed description, with appropriate reference to the accompanying drawings.

BRIEF DESCRIPTION OF THE DRAWINGS

Exemplary embodiments of the present invention are described herein with reference to the drawings, in which:

Figure 1A is a perspective view of a microscope system in an embodiment of the invention, in combination with other components such as a display, barcode reader, and slide magazine;

Figure 1B is a perspective view of two microscopes in another embodiment of the invention;

Figure 2A is a side cutaway view of a guidance system for a microscope assembly according to an embodiment of the invention;

Figure 2B is a front cutaway view of the guidance system, a stage and light assembly of the microscope assembly shown in Figure 2A;

Figure 2C a side cutaway view of position switches in the microscopic assembly;

Figure 2D is a front cutaway view of a lower portion of the microscope assembly shown in Figure 2B;

Figure 2E is a side cutaway view of the stage, including a z-axis plate, of the microscopic assembly shown in Figure 2A;

Figure 2F is a top cutaway view of the stage of the microscopic assembly shown in Figure 2A;

Figure 2G is a top cutaway view of the microscope assembly shown in Figure 2A;

Figure 2H is a front cutaway view of the microscope assembly shown in Figure 2A;

Figure 2I is a side cutaway view of the microscope assembly shown in Figure 2A;

Figure 3A-3D are cutaway views of the focus drive and switches of the microscope assembly shown in Figure 2A;

Figure 4A is a side cutaway view of the centralized filament, mirrors and lenses of the microscope assembly shown in Figure 2A;

Figure 4B is a cutaway view of the light source assembly shown in Figure 4A;

Figure 4C is a block diagram of the light feedback system for the light source assembly shown in Figure 4A;

Figure 4D is a flow chart depicting operation of the light feedback system shown in Figure 4C;

Figure 4E is a diagram of a color temperature measurement system employed in an embodiment of the invention;

Figure 4F is a graph of current versus wavelength to determine the color temperature;

Figure 4G is a flow chart illustrating steps for determining and modifying the light level in a microscope system according to an embodiment of the invention, in order to facilitate operation at a predetermined spectral distribution;

5 Figure 5A is a fixed condenser geometry of an imaging system configuration of the microscope assembly shown in one embodiment of the invention;

Figure 5B is a top cutaway view of the fixed condenser geometry of Figure 5A;

Figure 5C is a side cutaway view of the fixed condenser geometry Figure 5B;

10 Figure 6 is a side cutaway view of a microscope assembly and imaging system according to another embodiment of the invention;

Figure 7 is a perspective view of the base and bridge of the microscope assembly;

Figure 8 is a side cross-sectional view of the microscope assembly including the bridge, base and optical center line;

15 Figure 9A is a perspective view of the Z-axis plate, guideposts, spacer post, bushings, lower plate and collar of the microscope assembly;

Figure 9B is a cross-sectional view of the Z-axis plate, guideposts, spacer post, bushings, lower plate, collar, base and elevation screw of the microscope assembly;

Figure 9C is a top view of the collar;

20 Figure 10 is a cross-sectional view of the Z-axis elevation screw drive including the nut, elevating screw, collar, radial bearings, thrust bearing and base;

Figure 11A is a perspective view of a microscope system in an embodiment of the invention which includes a rotating wheel; and

Figure 11B is a top view of the rotating wheel with slots.

The microscope may be used in combination with a detector for sensing the magnified image of the sample, as discussed subsequently with respect to Figure 6. In one embodiment, the detector is a high resolution, scientific grade charge coupled device ("CCD"), such as may be used in a video camera. However, the invention is not limited to use of a CCD, but may use other means for capturing or viewing an image. Such devices may include, for instance, in addition to CCD cameras and traditional video cameras, photomultiplier tube (PMT) assemblies. The camera is preferably affixed to a video-port on top of the eyepiece of the microscope in order to capture cell images. A variety of cameras are available, depending on the resolution requirements (including spectral resolution, spatial resolution, photometric resolution and temporal resolution) of the user. Three available video cameras include the Pulnix TM-1001 available from Pulnix Corp. of Sunnyvale, California, the Kodak Megaplug ES1.0 from Eastman Kodak of Rochester, New York and the SMD 1M15 from Silicon Mountain Devices of Colorado Springs, Colorado. A lens with 10X magnification, 0.4 numerical aperture (other magnifications or numerical apertures may be chosen depending on the ultimate application), provides the combination of a large field of view as well as the high spatial resolution to facilitate efficient specimen screening by a single objective lens.

Images received by the camera are captured by a Data Raptor type frame grabber available from Bit Flow Corp., Woburn, Massachusetts, and transferred to an image analyzer for analysis. The microscope and image analyzer are coupled by a serial data link which permits the image analyzer to initiate control of an autofocus function on the microscope and to capture specimen position information. The microscope is preferably controlled by a controller board, which is described in further detail in U.S. Patent No. 5,930,732, entitled "System for Simplifying the Implementation of Specified Functions," the entirety of which is hereby incorporated by reference.

General Arrangement

Referring to Figures 1 and 2A-2G, there are shown various views of a microscope 10. In the exemplary embodiment, microscope 10 includes a number of sub-elements, including a base 12, a Z-axis plate 13, a Y-axis slide 14, an X-axis slide 15, magnifying lens(es) (such as objective 16), slide holder 19, eyepiece 20, and light source 77. The Z-axis plate 13 supports the slide containing the sample and can move the sample in the Z-direction, as shown in the Figures. As further shown in Figure 2F, the Y-axis slide 14 moves the sample in the Y-direction via a motor 43, and the X-axis slide 15 moves the sample in the X-direction via a motor 41. The slide is held in a carriage 45 which moves in the X-direction.

Base 12 provides rigid support for the microscope and, as shown in the Figures, may form the bottom portion of the microscope. In an alternative embodiment, the base may include an upper portion as shown in Figure 6, as discussed subsequently. Moreover, in Figures 2A-2D and Figures 2G-2I, the light source 77 is attached to the base and the path of light from the light source 77 travels through the base. In an alternate embodiment, the light source 77 may be attached to an upper portion of the microscope.

The controller board within the microscope 10 receives signals from the multifunctional control unit. The controller board preferably generates and transmits signals to control the operation and movement of the aforesaid components of the microscope, and to transmit and receive information generated by sensors on the microscope, via ports 66 as shown in Figure 2A, to and from the DMS. In some embodiments, the controller board may control the transmission and selection of information between the microscope 10, camera, frame grabber, image analyzer, and the DMS. In still other embodiments, the controller board may be used to control the operation and movement of the components of the microscope 10. The images received from the microscope 10 may also be selectively sent to a computer for processing. The controller board also controls the light level, the power turret, which selects the lens for viewing the sample, the stage translation speed, the spatial orientation of the sample on the Z-axis plate 13, the Y-axis slide 14 and the X-axis slide 15, and the intensity and color temperature/illumination control.

Referring to Figure 2C, there is shown a side cutaway view of the lower portion of the microscope including position switches 58. Included in this portion is the stage 27, which is shown as side and top cutaway views in Figures 2E and 2F, respectively. The stage 27 typically is the portion of the microscope that provides movement of the sample. The stage 27 may move upward and downward during focusing and may include a plate, such as a Z-axis plate 13. A plate may be an object that, either directly (by direct physical contact) or indirectly (through another object), holds the sample. In a preferred embodiment, the stage 27 includes the Z-axis plate 13, the Y-axis slide 14, the X-axis slide 15, the condenser lens system 29, and guideposts 55. As discussed subsequently, the Z-axis elevation system employs an elevating screw which is in contact with the lower portion of the Z-axis plate 13. Moreover, movement in the x-direction and y-direction is performed by motor 41 and motor 43, respectively.

Vertical Movement and Guidance of Microscope Stage

Because of the design of the present invention, the microscope 10 is very precise and accurate. The improved microscope 10, for instance, enables a cytotechnologist or other observer to rapidly, precisely and accurately locate objects of interest with the requisite positional accuracy and precision, e.g., in cytological applications, within ± 5 microns. In addition, the microscope of the present invention may be manufactured at a moderate price while still maintaining high precision. In particular, the invention permits development of a system of precise tolerance components which, when assembled with a thermoset plastic material, yields the required performance accuracy. In addition, the system has proven to be dimensionally stable. In order to achieve a level of accuracy and stability similar to the present invention, a conventional microscope would require extremely precise components, rendering the cost of the microscope financially impractical.

The stage 27 is moved along the Z axis by a device that applies force at a specific point on an underside of the Z-axis plate 13. As discussed subsequently, the Z-axis elevation system employs an elevating screw 89 which is in contact with the lower portion of the Z-axis plate 13. The force is preferably applied at a single point via the elevating screw 89, which, in a preferred embodiment, works in combination with a motor assembly. The elevating screw 89 is, in one embodiment, 8 mm in diameter with a .5 mm pitch. This placement of a single, specific point of force on the Z-axis plate 13 of the stage provides for greater stability when moving the stage 27. If a single point of force for moving the stage 27 is chosen, it is preferably applied at, or substantially at, the center of gravity of the stage 27 in order to reduce the amount of geometric errors. This configuration improves over typical microscopes, in which the manner of moving the stage is to apply force to the plate at points that are not at the center of effort or gravity. For example, a typical cantilever bearing system (commonly referred to as the knee and column design) may increase the possibility of geometric errors while viewing due to the offset manner of moving the stage. Moreover, as the inventors have discovered, this prior art method creates instability while moving the stage.

According to the current method and apparatus, the force for moving the stage upward and downward is concentrated at the center of gravity 139 of the stage (which includes the X-axis slide 15, Y-axis slide 14 and Z-axis plate 13), as shown in Figure 2G. In this manner, the point of force for moving the stage is preferably limited to a single point, typically the center of effort. In an alternative embodiment, there may be a multitude of forces applied at various points on the plate to move the Z-axis plate 13 (and in turn the stage 27) upward and

downward. The net effect of these forces is that there is an upward or downward force at, or substantially at, the center of gravity of the stage. For example, a multitude of forces may be applied at different points on the stage, with the net force being at the center of gravity of the stage and in the Z direction or in the direction of the optical path. In addition, the application of force at this point inherently maintains stability of the system during movement. The device, or "forcer," that is used to apply force to one point may take a variety of forms. As examples, the forcer may take the form of a piston, lead screw, finger, lever, column, cam, gear system using rack and pinion, or piezoelectric device or voice coil. Referring to Figures 2H and 2I, there are shown front and side cutaway views of the microscope assembly.

In the exemplary embodiment, the arrangement for vertically moving stage 27 advantageously takes the form of a single jack screw sitting in a radial/axial thrust bearing system. Referring to Figures 3A and 3B, this arrangement is shown in more detail as apparatus 56 located beneath the Z-axis plate 13. The assembly of this apparatus contains radial ball bearings 57 and nut 87 fixed within the bearings 57. Specifically, ball bearings 57 have an inner race in contact with nut 87 and an outer race in contact with base 12 (so that the outer race does not move). An elevating screw 89, which is in contact with the Z-axis plate, engages nut 87.

The Z-axis plate 13 is gravity-loaded against a thrust bearing for the elimination of focusing hysteresis (backlash) while moving the Z-axis plate 13. In an alternative embodiment, the elevating screw, or other means for applying force at one point to the Z-axis plate 13, may be attached to the Z-axis plate 13. A synchronous timing belt and pulley system 61 coupled to a motor 59. As shown in Figure 3A, the motor 59 is adjacent to the ball bearings 57 and nut 87. Thus, when the Z-axis plate is to be moved vertically, the motor assembly 59 moves the pulley 61, which then turns the nut 87 and the inner race of bearings 57. The nut 87 in turn moves the elevating screw 89. Via a coupling 103, the elevating screw 89 moves the Z-axis plate 13. In the exemplary embodiment, the elevating screw is an 8 mm diameter hardened ball screw with a pitch/lead of 0.5 mm, and the net result of the gear reduction is that one microstep (or one step of the motor) equals 1/16 micron elevation of the stage.

The screw may be made of a heat treatable steel such as Timken ball bearing steel (AISI-52 100). Preferably, the elevation screw, the nut and the balls are all made of the same material, treated to a high level of hardness, such as Rc-62/64. In that way, it is believed there will be no possibility of brinelling (i.e., the disruption of smooth surfaces from interplay

between components), which could otherwise interrupt the smooth rolling of balls 57 and give rise to abrupt motion.

As thus shown and described, in the exemplary embodiment, the arrangement of components that move the stage vertically, i.e., the elevating screw 89, the nut 87, and the bearings 57 (as well as a portion of pulley assembly 61), forms a single-column assembly. As further shown in Figure 3A, this single-column assembly is rigidly mounted to base 12 by bosses 35, which is a raised surface that is part of the base 12, machined to accept the single column assembly.

Further, this single-column arrangement is itself inherently very rigid compared to the typical microscope focus systems, which usually employ gear box designs. In traditional arrangements, a focus system may go through a 12-14 gear reducer system, which normally has large hysteresis, play, lash and spring. With such systems, manufacturers typically cannot guarantee less than 5 micron hysteresis. With the present jack screw arrangement, in contrast, dramatically fewer parts are required. In effect, the screw 89 itself can be static (except for up and down movement), and the only moving part might be nut 87, which rotates in the radial axial bearing arrangement. Advantageously, this arrangement should be able to provide closer to 1/16 micron or better hysteresis, a significant improvement over the existing art.

Turning back to Figure 2G, there is shown the motor assembly 137 that applies a point of force on the Z-axis plate 13 at the center of gravity 139 of the Z-axis plate 13. In an alternate embodiment, as shown in Figure 3B, the motor assembly may be offset from the center of gravity of the Z-axis plate 13.

The stage 27 theoretically does not require anything for operation in addition to the elevating screw 89 and the associated motor assembly. This is due to the fact that the elevating screw 89 moves the stage 27 at its center of gravity. However, on a practical level, the stage 27 may experience movement in the X and Y directions during operation. For example, the elevating screw 89 is designed to provide thrust in the Z-direction. In addition to the thrust, there may also include lateral movement in the X- and/or Y-direction. In order to reduce or minimize this movement, a guidance system is used. The guidance system assists in maintaining proper alignment of the stage 27 with respect to the optical axis. The guidance system of the microscope of the present invention is preferably centered or substantially centered around the optical path through the Z-axis plate 13 of the microscope. An optical path is defined as the path through which light passes through the microscope.

One portion of the optical path is through the stage 27 of the microscope. Of primary importance are the stability and geometric accuracy of the system at the optical path. According to a preferred embodiment, this stability may be achieved by centering the guideposts around the optical path. This is in contrast to guidance systems of typical
5 microscopes, which are not centered around the optical path of the microscope and which may have an overhang of components. These existing systems are typically unstable and are thereby prone to producing yaw, pitch and droop errors of the stage (and therefore the image) due to a lack of stability in design.

In an exemplary embodiment, the method for guiding the Z-axis plate 13 is via a
10 plurality of guideposts 55, as shown in Figures 3A-C. Each of the guideposts 55 is preferably equidistant from and approximately symmetrically placed around the optical path through the Z-axis plate 13. As shown in Figure 2G, the center of the locus of points of the guidance system for the Z-axis plate 13 and stage 27 is coincident with the optical path. For example, the guidance system may be clustered in an array, with the array being any number greater
15 than one. The center of that array should be coincident with the optical path. So that, if one takes a cross-section of the guidance system perpendicular to the optical path, that center of the array is at or substantially at the optical path.

The guidance system in one embodiment includes two portions, one portion being a part of or attached (either removably or permanently) to the stage or the plate (such as the Z-
20 axis plate) and the other portion being a part of or attached (either removably or permanently) to the base. For example, in one embodiment, the guideposts 55, which are attached to the Z-axis plate 13, are the first portion and ball bushings 54, which are attached to the base 12, are the second portion. The guideposts 55 and the ball bushings 54 mate with each other to stabilize movement, and are discussed subsequently with respect to Figures 3A-D. The
25 guidance system in another embodiment includes two portions, one portion being an integral part of the stage or plate and the other portion being an integral part of the base. For example, the Z-axis plate may have holes which engage guideposts that are integral with the base or are affixed to the base. In an alternative embodiment, a plurality of guideposts at varying distances from the optical path are used. In particular, a first set of guideposts is a
30 first predetermined distance from the optical path (with each guidepost being at the same first predetermined distance from the optical path) and first angular disposition (the guideposts being distributed around the circumference of the optical path), whereas another set of guideposts is at a second predetermined distance from the optical path (with each guidepost

being at the same second predetermined distance from the optical path) and second angular disposition (the guideposts being distributed around the circumference of the optical path).

Referring to Figures 2E and 3A-D, there are shown cutaway views of the focus drive and switches of the microscope assembly. Three bore holes 51, 52 and 53, discussed subsequently, are placed in the Z-axis plate as shown in Figure 2G. Moreover, recirculating ball bushings 54, as shown in Figure 3A, are attached to the base 12 and are preloaded into the bore holes 51, 52, 53 of the Z-axis plate. The recirculating ball bushings 54 act as guidepost mates that engage the guideposts 55. Guideposts 55, preferably machined to a tolerance of millionths of an inch, are affixed to the bore holes 51, 52, 53 and run in the bushings 54. The bushings 54 and the guideposts 55 are designed such that they operate with essentially zero clearance. In particular, the bushings 54 contain bearings that are rolling balls operating in an interference mode with the guideposts 55, so that there is no off-axis motion. Thus, the movement of the stage 27 is vertical with no lateral play. Due to this design, the stage 27 may operate with vertical movement typically in 1/16 micron increments. Other types of guidance systems, such as a linear bearing system, flexure plates, air or magnetic bearings or a dovetail slide with gibs system, are possible as well. Moreover, as shown in Figure 3C, one of the guideposts 55 is extended in length so that at a certain level, the guidepost engages switches 58. The switches 58 thereby may indicate the position of the Z-axis plate 13.

Referring to Figures 2A-C, there is shown side, back and top cutaway views of the microscope assembly, respectively. The optical microscope 10 includes a stress annealed aluminum Z-axis plate, having precision bored holes 51, 52, 53. These holes are preferably bored with a key tolerance of about 10 microns. The number of bored holes may vary depending on the mechanics of the microscope assembly. The heat treating of the cast aluminum member increases dimensional stability. In addition, the precision bored holes allow the Z-axis plate 13 to move along the optical path in a smooth manner, i.e., without jittery, shaking or jerky motions, during scanning and focussing. The Z-axis plate 13 is preferably cast aluminum, which may be rough machined. Then, the Z-axis plate 13 may undergo heat treatment for stress relief. Thereafter, the holes may be precisely bored into the Z-axis plate 13 so as to be aligned accurately and non-changeably with time. Therefore, due to the centration of the guidance system around the center of gravity, errors of droop, pitch and yaw tend to nullify or to cancel themselves to zero.

Light Source Alignment and Emission

Referring to Figure 4A, there is shown a side cutaway view of the centralized filament, mirrors and lenses of the microscope assembly. Condenser lenses 63, 65 receive light through a numeric aperture diaphragm 67, which in turn receives light through a mirror system 69, through a field diaphragm 71, a filter diffuser 73, a second mirror system 75, a second filter diffuser 76. Light is generated by a halogen light source or any other light source with a centralized photon emitter (*i.e.*, illumination source). Means have been developed for a photon emission module to be easily replaced without the necessity of complicated or costly efforts at realignment of parts or processes, as discussed subsequently.

In addition, light may be generated from any light source whose photon emitter (*e.g.*, filament) is at a predetermined location from the base, screw or other mounting geometry of the light source. Once the base or other mounting geometry is properly aligned, the photon emitter is likewise aligned with the optical path due to the predetermined nature of the light source. The optical alignment is therefore obtained by machining components rather than by adjusting the light source, thereby minimizing error. In the case of a centralized photon emitter, the photon emitter is centered with the base or other mounting geometry of the light source.

Such an automated system requires precisely defined illumination. Such defined illumination is required when the system is initially used, throughout the life of use of the lamp (which may decrease in its illumination over time), and throughout the life of any replacement lamps. The present invention thus maintains consistent and precise illumination throughout use of the microscope. In conventional systems, when a light source is initially installed or replaced, the system must be realigned by a technician in order to minimize uneven illumination which may be received by the camera. In an embodiment of the current invention, the design of the system and the light source are such that the system is pre-centered due to the predetermined spatial relationship of the photon emitter with the mounting geometry of the light source and due to the mounting mechanism for the light source on the microscope. Thus, when a light source burns out, replacement of the light source automatically centers the photon emitter, as described below (within 2 thousandths of an inch of the theoretical center line).

Referring to Figure 4B, there is shown a cutaway view of the light source assembly. The light system is unlike a conventional microscope light source configuration, at least in part, since it has a photon emitter that is at a predetermined spatial location relative to a reference feature of its housing (*e.g.*, the base 92 or the mounting mechanism for the light

source) and due to the mounting mechanism of the microscope. In a preferred embodiment, the light source 77 is a halogen light source with a photon emitter 94 that is at a predetermined spatial location with the base 92, due to precise and accurate manufacturing of the light source. The distance from the base to the photon emitter is 20 millimeters in the
5 Welsh Allen, part no. 1036-1. Since the light source 77 is designed to have a photon emitter 94 at a predetermined axial and radial distance from the base 92 of the light source, the base 92 may be correctly positioned thereby correctly positioning the photon emitter. In this manner, the design of the illumination system enables lamps to be installed with near perfect centration.

10 In the present invention, any light source may be used, depending on the power requirements, so long as the photon emitter, or the means for generating the light, is at a predetermined axial distance from the base of the light source (i.e., the predetermined distance from one light source to the next is the same within an acceptable tolerance). In a preferred embodiment, a halogen light source is used. In addition, a light source in
15 combination with a fiber optic cable, an incandescent light source, a light emitting diode (LED), an arc lamp (e.g., xenon arc lamp or mercury arc lamp), or other such light source (with or without wavelength selection means) may be used.

The optical path 96 of the system is designed to be directed from the center of the halogen light source with a centralized photon emitter or filament. Therefore, the halogen
20 light source with a centralized photon emitter sends light directly (and with minimal shadowing) onto the physical image on the slide. In particular, in a preferred embodiment, the lamps are manufactured by Welsh Allen, part no. 1036-1, 30 watt halogen light sources with a centralized photon emitter. The housing 79 that receives the lamp is also designed such that the halogen light source with a centralized photon emitter 77 may be placed with
25 maximum accuracy and placement reproducibility. In this manner, when the base of the light source is positioned properly, the photon emitter of the light source is positioned properly as well.

The housing 79 contains a mounting mechanism for receiving the light source. The mounting mechanism is designed to receive the light source 77 precisely, both concentrically
30 and axially. The mounting mechanism, in one embodiment is an accurate and precise boring of a hole 91 in the housing 79. Other mounting mechanisms, such as clamps, may be employed wherein the mounting mechanisms concentrically and axially place the light source in housing 79.

In addition, the hole 91 is of sufficient axial and radial positional accuracy to provide the imaging system with a positional tolerance of about 0.127 millimeters. This precision boring receives the base 92 of the light source. In addition, a seat 95 is precisely bored and/or shaved so that the base 92 of the light source abuts the hole 91 in perfect alignment. The precision boring of the hole 91 and the seat 95 thereby ensures that the base of the light source 77 is in its proper placement. In addition, a threaded hole 98 is bored to engage the screw mount 100. The screw mount 100 attaches the light source 77 within the housing 79 and makes electrical contact with the compliant contact 102 in the housing 79. Because the photon emitter is at a predetermined location relative to the base, the photon emitter of the light source 77 is in proper alignment and centered at the optical center line. Power is connected to the light source 77 via wires 97 and a connector 99.

In addition to proper placement of the light source, the intensity of the light source can be controlled. In both an operator driven system (in which, for example, the operator views the magnified image through an eyepiece in the viewer) and a detector based system (in which, for example, a detector, such as a camera, receives the magnified image from the viewer and acts as an electronic image viewer), the proper amount of light can be generated to illuminate the sample. In particular, in a detector based system, the detector may have an optimal light level (or optimal light range) under which it operates. For example, when using a camera, the camera has a range of optimal values of light for operation. When the camera receives an image with less than the optimal value of light, it adjusts the shutter speed to lengthen the exposure time. Similarly, when the camera receives an image with more than the optimal value of light, it adjusts the shutter speed to shorten the exposure time. To better capture the image from the detector, the light level should therefore be chosen so that the detector operates in its optimal light range.

In order to accomplish this, a detector is used to sense light that is in the optical path 96. The light travels from light source 77 and is ultimately sent to the viewer. As shown in Figure 4A, the light travels from the light source 77 to the second filter diffuser 76 to the second mirror system 75 to the filter diffuser 73 to the field diaphragm 71 to the mirror system 69 to the numeric aperture diaphragm 67 to the condenser lenses 63, 65. In order to determine the intensity level of the light, the light may be sensed at any point in the path of the light source through the microscope. In Figure 4a, the mirror system 69 is a 98/2 mirror that reflects 98% of the incoming light and passes 2% of the light. Behind the mirror system 69, a detector in the form of light intensity monitor system 101 senses light that passes

through the mirror system 69. The light intensity monitor system 101 is an electronic component such as a diode that feeds back information to the computer system or processor, which controls the light level of the lamp, as described subsequently. In addition, any form of light detector may be used to sense the light.

5 There are methods in which to both sense and control the intensity of the light. Referring to Figure 4C, there is shown a block diagram of one preferred embodiment of the light feedback system. The light source 77 generates the light and has a power sub-block 111. In one possible embodiment, the power sub-block 111 includes wires 97 and connector 99, which connects to one end of the light source 77. The light is sensed by a detector 105.
10 The detector 101 sends its output to a processor 105, which contains a comparator 107 and a look-up table 109. The look-up table 109 may take the form of a permanent memory such as read only memory (ROM) or a temporary memory such as random access memory (RAM). Depending on the operation of the processor 105, described subsequently with respect to Figure 4C, the processor alters the amount of power to the light source in order to adjust the
15 level of illumination.

Referring to Figure 4D, there is shown a flow chart for determining and modifying the light level in the microscope system to operate at a precise amount of illumination. A portion of the light that is generated from the light source is sensed via a detector, as shown at block 113. This value is sent to the processor 105, which determines whether the amount of light
20 generated is within the optimal range. In particular, the processor determines whether the light is greater than the upper bound of the optimal range, as shown at block 115, or whether the light is less than the lower bound of the optimal range, as shown at block 121. In the preferred embodiment, as shown in Figure 4A, because of the 98/2 mirror 70, the detector 101 senses 2% of the light. Therefore, the processor 105 is able to determine, based on the
25 sensed light, how much light is being generated. In addition, the light may be sensed at any point in the optical path, from near the photon emitter 94 of the light source 77 to the condenser lenses 63, 65.

Look-up tables 109 in the processor 105 have a first predetermined value and a second predetermined value. These values define the amount of sensed light from the
30 detector when the light source is operating in the upper limit of the optimal range and the lower limit of the optimal range, respectively. In addition, these predetermined values may be generated during calibration of the microscope. The first predetermined value indicates that the amount of light in the microscope is at the upper limit of the optimal range and the

second predetermined value indicates that the amount of light in the microscope is at the lower limit of the optimal range. Using the comparator 107, the sensed light is compared with the first predetermined value to determine if the sensed light is greater than that value, as shown at block 115. If it is, then too much light is being generated by the light source and the amount of power to the light source should be reduced. The sensed light is also compared to the second predetermined value to determine if the sensed light is less than that value, as shown at block 121. If it is less, then too little light is being generated by the light source and the amount of power to the light source should be increased.

To regulate the amount of power to the light source, the processor first determines the amount of power that is currently being given to the light source, as shown at block 117. In one embodiment, this is done by sensing the amount of current sent to the light source. In another embodiment, the processor has the value of the amount of power that corresponds to the amount light detected stored in the look-up table. If the sensed light is greater than the first predetermined value, the amount of power to the light source is reduced, as shown at block 119, corresponding to the amount of the sensed light that is greater than the first predetermined value. On the other hand, if the sensed light is less than the second predetermined value, the amount of power to the light source is increased, as shown at block 125, corresponding to the amount of the sensed light which is less than the second predetermined value. In an alternate embodiment, the light level is adjusted, either upward or downward, by incrementing the current to the light source upward or downward. This determination of the light level in the optical path is preferably continuous when the machine is in use.

In addition to controlling the intensity of the light source, the spectral distribution of the light source should be controlled in order to obtain the proper color-fidelity image. Imaging systems, such as photographic film or cameras, have a certain spectral distribution in which they best operate. In order to obtain the best image from the imaging system, one must choose the illumination from the light source in order to be within the optimal spectral distribution of the imaging system. In addition, analysis of specimens may be spectrally based. In those instances, the correct spectral distribution removes potential error based on varying illumination.

One measure of the spectral distribution is the color temperature. The color temperature is a measure of the intensity of the light at different wavelengths. Therefore, analysis of the color temperature indicates the spectral distribution of the light in the

microscope. In an alternative embodiment, the spectral distribution may be sensed at a band of wavelengths or across the entire electromagnetic spectrum.

Typically, an incandescent light source shifts its spectral distribution of the light (and hence its color temperature) when the light source increases or decreases illumination. At the lowest illumination levels, the majority of the incandescent light may be in the infrared light range. As the illumination increases, the peak of the wavelength shifts to the visible light range eventually shifting to the ultraviolet light range.

In order to maintain proper illumination during operation of the microscope, the proper illumination is determined during initial calibration of the microscope. Also, during calibration, measurements are taken at wavelengths to determine the proper intensity at the wavelengths for the proper illumination. Thereafter, during operation, the intensity is tested at the wavelength(s) to determine whether the intensity of the light source should be increased or decreased.

Referring to Figure 4E, there is shown a diagram of a spectrum distribution measurement system that measures color temperature. The incoming light is sent to a dichroic beam splitter 141, which splits the light into two parts with high efficiency. Other forms of beam splitters may be used depending on the efficiency necessary. The split beams are then sent to wavelength selection filters 143, 145 whereby a narrow band of wavelengths are passed. Thereafter, the filtered light is sent to Detector λ_1 147 and Detector λ_2 149 which generates a current (or voltage depending on the sensing circuit) as a function in the corresponding wavelength. Detector λ_1 147 and Detector λ_2 149 in one embodiment are both photodetectors (e.g., diodes). In another embodiment, the selection filters and diodes may be integrated into one package. Further, in a preferred embodiment, the selection filters and detectors are placed closer, and sense light closer, to the light source 77. In an alternate embodiment, selection filters and detectors are placed closer to the condenser lenses 63, 65 in order to sense any changes in the spectral distribution as light travels through the microscope system.

A graph of a spectral distribution of current (I) versus wavelength (λ) for two different illuminations is shown in Figure 4F. Referring to Figure 4G, there is shown a flow chart for determining and modifying the light level in the microscope system to operate at a predetermined spectral distribution. The color temperature is proportional to $I_{\lambda_1}/I_{\lambda_2}$. Therefore, in order to determine the change in color temperature (and hence spectral distribution), the present measurement of the proportion is compared to the proportion

measured during calibration of the system (when the system was operating with an optimal spectral distribution). The amount of light is sensed at certain wavelengths, λ_1 and λ_2 , as shown in block 151. Depending on the amount of light sensed, currents are generated in the detectors, as shown in block 153. Depending on the comparison between the outputs of Detectors λ_1 and λ_2 , and a value which is determined during calibration, the current or voltage of the light source is modified, in order to maintain a constant color temperature (and hence constant spectral distribution). For example, if λ_1 is greater λ_2 , and the current proportion of $I_{\lambda_1}/I_{\lambda_2}$ is less than the calibrated proportion (which is stored in the same look-up table, or similar look-up table as the table 109 in Figure 4C), as shown in block 157, the spectral distribution is too far into the infrared range, so the illumination should be increased (by increasing the voltage or current), as shown in block 159. Likewise, if the current proportion of $I_{\lambda_1}/I_{\lambda_2}$ is greater than the calibrated proportion, as shown in block 161, the spectral distribution is too far into the visible region or ultraviolet range, so the illumination should be decreased (by decreasing the voltage or current), as shown in block 163. In this manner, constant color temperature may be maintained in order to optimize the use of the imaging system and maintain the integrity of spectral-based analysis.

As discussed previously with respect to Figures 4A-4D, the intensity of the light source may be controlled by varying the current (or voltage) to the light source. The greater the intensity desired, the higher the current (or voltage). However, when attempting to integrate control of both intensity and spectral distribution (or color temperature), means other than modifying the intensity at the light source are used to control the intensity. For example, one may separate the two functions by controlling the color temperature through the adjustment of the lamp power and by controlling the intensity by using crossed polarizers in the optical path. Depending on the intensity required, the polarizers may be turned to modify the intensity of the light. If polarized light is not conducive to the imaging system, a polarizer scrambler may be used in combination with the polarizers. Other means may be used to shield a portion, or all, of the light in the optical path without altering the power to the light source. Another method to modify the intensity without influencing the color temperature is through neutral density filters. Moreover, any means known to those skilled in the art that does not influence the spectral distribution or color temperature but affects the intensity may be used.

In an alternate embodiment, a selection filter placed in front of the detector 101 for the intensity illumination in Figure 4A may sense data both for color temperature and for

intensity. The single detector may sense the intensity at one wavelength. Assuming a constant spectral distribution for a variety of intensities, both the intensity and the color temperature may be determined. Moreover, in an alternate embodiment, a wavelength selection means 72 which selectively passes a single wavelength or a band of wavelengths may be placed anywhere the optical path.

Referring to Figure 5A, in one embodiment of the invention that is of particular utility in an automated system, there is shown a fixed condenser geometry of an imaging system configuration of the microscopic assembly, as used in the automated sample analysis system 23 in Figure 1B. In systems which are completely automated, the optics are designed with fixed rigid optics that are prealigned. During initial calibration of the microscope, the placement of certain optics, including the condenser lens(es) and the numerical aperture, are fixed. Therefore, once assembled, aspects such as the focus, the diaphragm size, the aperture, etc. are fixed. Figure 5A is shown with the lenses all fixed in locations by a condenser lens body 80. Once built, the lenses cannot change in position.

In order to design a system that may be configured as a fixed optic system, a portion of the optical system, as shown in Figure 4A may be designed with the fixed optics, as shown in Figure 5A. The optical system is reconfigured with lens focusing and pupil apertures all established by machined and locked settings during initial calibration of the microscope. This insures that the system is always in the calibration established at the time of setup. Referring to Figure 5A, the condenser lenses 63, 65 in one embodiment may be fixed rigidly to the microscope. Also shown is the objective 16, which is one type of magnification lens. Condenser lens 63 and condenser lens 65 are placed within a housing 68, as shown in Figure 5C, a predetermined distance apart using spacers 81 to maintain the separation. In addition, numerical aperture 67 has a fixed pupil and is held rigidly by abutting the numerical aperture 67 against a ledge 86 and placing a snap ring 83 to hold the numerical aperture 67 (with a fixed aperture) rigidly in place. The ledge 86 may be machined in order to properly align the numerical aperture 67 during calibration of the microscope. Another ledge 85 may be machined in order to affix the assembly with the condenser lenses 63, 65 and numerical aperture 67. Mounting screws 88 are used to adjust the fit, which is thereafter permanently affixed by pins 90, as shown in Figure 5A and 5B, so that condenser lens body 80 is attached to the Z-axis plate 13. In this manner, the condenser lenses 63, 65 and the numerical aperture 67 are permanently in focus and do not require adjustment. Further, the field diaphragm 71 is fixed to the base, as shown in Figure 2G, and has a fixed pupil. In an alternative

embodiment, for a light source that is not attached to the base, the field diaphragm may be attached to a portion of the microscope other than the base. However, the field diaphragm still has a fixed pupil.

Imaging System

5 Referring to Figure 6, there is shown a side view of a microscope with an attached imaging system. In one embodiment, the imaging system is a camera 127. The imaging system is affixed to the microscope, according to one embodiment, at two separate places. The first place is at the viewer portion of the microscope. The camera mounts to an extender portion 129. The extender portion 129, in one embodiment, is L-shaped with one end being
10 connected to the camera via a screw thread C-mount 131 and the other end being connected to the microscope via a dovetail portion 133. In addition, the camera 127 is attached to the body of the microscope at a second place along the upper microscope housing 138 of the camera itself. Referring to Figure 6, there is shown a second connector, which, in one embodiment is a dovetail portion 135 that is connected to one side of the camera 127. The
15 second connector is also connected to an intermediary piece 137, such as a shim. The intermediary piece is connected to the body of the microscope. In this arrangement, the camera is first aligned via the extender portion 129 and thereafter the camera body is rigidly fixed to mounting surfaces provided on the microscopy frame. The camera is therefore rigidly fixed to the microscope so that during operation, the camera will not be moved out of
20 alignment. The camera may be rigidly fixed to the microscope in more than two places,

Connection to External Systems

Moreover, according to a preferred embodiment, the microscopy system is designed to be integrated into a larger system containing additional components. The microscopy system includes mounting geometry and electrical connections sufficient to allow
25 incorporation into other instruments. The imaging system may therefore be designed to minimize problems with interconnections to other devices such as computers and the like. The imaging system includes a connector 62, as shown in Figure 2A and 2C. The system is designed with a centralized circuit board 64 which, in turn, is connected to the connector 62. The connector 62 provides data transmission to such components as the DMS discussed
30 above as well as electrical connections. The system may also have fixtures with mounting surfaces for the placement of accessories (such as a laser bar code reader). The added structure provided by these fixtures enhances the stability and thus the accuracy of the system. As shown in Figures 2A and 2C, there are ports 66 that provide a connection for all

of the on-board systems for the microscope. The ports 66 allow for the connection to other units that may work in combination with the microscope. For example, other devices, such as a dotter, bar-code reader, power lens turret controller, slide sensor and camera controller, etc. may be in communication with the microscope and imaging system via the ports 66, for instance.

Bridge Frame

The microscope assembly described above advantageously provides for increased stability and precision. In the arrangements described above, however, the microscope frame structure is illustrated as a "C" frame or cantilevered design, which is primarily dictated by a need to provide operator access to the specimen from the front of the microscope, effectively through the open side of the "C" structure. Unfortunately, when a microscope is used for quantitative imaging operations, it has now been determined that the instability of the cantilevered design begins to limit the efficacy of the system. Movement caused either within the system (such as vibrations caused by a motor within the microscope) or outside the system (building shaking or heating/air conditioning system) effect the operation of a typical cantilevered system. In particular, this type of structure does not have a good dynamic stiffness. Dynamic stiffness is a measure of the dynamic response of the microscope (*i.e.*, a measure of how the microscope reacts to live loads such as how much the microscope shakes, vibrates or deflects). Microscopes which magnify an image to a great degree should have a sufficiently good dynamic stiffness, particularly at the optical center line. Otherwise, the microscope will shake or move to such an extent that the microscope will not be able to capture a clear image. However, the current "C" structure allows for too much variations, especially at the optical center line, limiting the ability of the imaging system to realize the maximum resolving power of the sensing elements.

According to an additional aspect of the invention, microscope stability can be further enhanced by including structure which increases the dynamic stiffness of the microscope with a focus on the dynamic stiffness at the optical center line. One example of the structure is shown in Figures 7 and 8. Referring to Figure 7 and 8, a brace 200 is rigidly connected between the upper portion 210 of the microscope assembly and lower portion 212 of the microscope assembly, thereby making the overall microscope frame structure a closed ring (from a side view). The brace 200 is designed to work in conjunction with the upper portion 210 of the microscope assembly to make the microscope more stable during operation. In turn, rather than mounting optical elements (such as a camera, for instance) on top of a

cantilevered structure, the optical members are instead preferably mounted at the center on what is effectively a "bridge" structure, supported on one end 214 by the brace and on another end 216 by the "back" side of the microscope frame. In the exemplary embodiment, these supporting structures on both sides of the optical element carrier (i.e., the bridge) have substantially the same tensile and compressive characteristics as each other, thereby enhancing stability.

The structure of brace 200 is designed to afford the requisite stability. The brace 200 should be close to the optical center line, without interfering with the movement of the stage in either the z-direction or y-direction. To accomplish this, the brace 200 is composed of two portions, lower portion 218 and upper portion 220. Lower portion 218 meets upper portion 220 at surface 222. The innermost portion of surface 222 is point 224 which is adjacent to the stage, but not touching the stage, when the stage is in its outermost position (i.e., the stage is in its uppermost z-position and in its greatest y-position).

Moreover, the cross-sectional area of the brace 200 is designed to afford the requisite stability. This is due to the fact that the corresponding microscope structure without the brace was exhibiting movement only in the z-direction. To provide additional stability in the z-direction, the brace has a rectangular cross-section, as shown in Figures 7 and 8. Alternatively, if the microscope exhibits movement in the z-direction and x- or y-directions, the cross-section of the brace is correspondingly modified in order to provide stability in each direction. For example, if there is vertical (z-direction) and lateral (x- and/or y-direction) movement, the cross-section of the brace may be composed of a "T" shape with the top portion of the "T" providing stability in the lateral direction. Alternatively, the cross-section of the brace 200 may be a hollowed section.

In order to empirically determine the shape of the cross-section of brace 200, measurements are first taken of the deflection of the microscope without brace 200. Varying weights (e.g., 1 lb, 5 lb, 10 lb, etc.) are placed on the upper portion 210 of the microscope (without the turret and eyepiece portion) at the optical center line. In a preferred embodiment, the amount of deflection of the upper portion 210 of the microscope is measured point 226, as shown in Figure 8. However, the amount of deflection can be measured at any point along the optical center line. Based upon these measurements, calculations are made to determine the thickness of the brace.

This arrangement affords a maximum stiffness consistent with the mass and modulus of the supporting material. In fact, this overall bridge frame arrangement is believed to

increase stability by over one order of magnitude (compared to the microscope frame without brace 200). For example, in one measurement, the amount of deflection was 20 μm without brace 200 and with a representative weight, while the amount of deflection with brace was less than 1 μm . Further, while brace 200 may somewhat block front access to the stage of the microscope system and to a specimen residing on the stage, such access is of decreased importance in automated imaging and screening systems, since it is rarely necessary for an operator to manually move the specimen on the stage. Nevertheless, in an alternative arrangement, the arrangement of Figure 7 could be varied to provide a plurality of braces from upper portion 210 to lower portion 212, or to provide a single brace with a front opening for operator access. In still an alternate embodiment, the supporting structure may be composed of an upper section of a sphere, with a hole in the top of the upper section where the optical center line passes through the turret.

In the exemplary embodiment, the connecting brace is cast as a loose piece and is then bolted to bosses that are integrally cast at the upper and lower portions of the basic "C" frame. The connecting brace is preferably cast of the same material as the rest of the microscope frame, so that it has the same thermal expansion and contraction characteristics. In the exemplary embodiment, this material is an aluminum alloy. Alternatively, the brace could be cast as an integral part of some or all other portions of the microscope frame.

Dual plate

As described above, with respect to Figure 3B for instance, the microscope system of an exemplary embodiment may include a Z-axis plate 13 from which three guideposts 55 extend into interference fit with bushings 54 that are attached to base 12. This arrangement provides for increased stability and accurate vertical movement of stage 27. However, if the guideposts are rigidly fixed only to the underside of the Z-axis plate, there is still a possibility that the structure might sway under some conditions. Moreover, if the elevating screw is in direct contact to the underside of the Z-axis plate, movement in the lateral direction is possible. Specifically, while the elevating screw is designed to direct force in the z-direction, unwanted force in the x- and/or y-direction is possible due to misalignment of the elevating screw.

To help minimize this possibility, still another alternative arrangement can be provided, as illustrated in Figure 9A. Referring to Figure 9A, an additional plate 216 is provided, fixed rigidly to the guideposts 55 preferably underneath the bushings. This lower plate functions to increase the stability and stiffness of the post and plate structure, effectively

creating an open box out of arrangement, and is believed to increase stability significantly. As shown in Figures 9A and 9B, the Z-axis plate 13 and the lower plate 216 are rigidly affixed to one another by guideposts 55 and by a spacer post 230. Ball bushings 54, which are affixed to the base 12, run in an interference mode with the guideposts 55. As shown in
5 Figures 3A-C, the ball bushings 54 are placed below the Z-axis plate 13. For additional stability, additional ball bushings 54 are placed directly above the lower plate 216. In the lowermost setting of the Z-axis plate, the distance 236 between the upper ball bushings and the Z-axis plate is minimal. Likewise, in the uppermost setting of the Z-axis plate, the distance between the lower ball bushings and the lower plate is minimal. This is to increase
10 the stability throughout the movement of the Z-axis plate.

The spacer post 230 is affixed to the Z-axis plate via a screw 232 and affixed to the lower plate 216 by a press-fit in an opening 238 in the lower plate 216. The spacer post 230 is positioned directly above the elevating screw 89, with a nub 234 on the top of the elevating screw 89 fitting in the lower portion of the spacer post 230. The spacer post 230 serves two
15 functions. First, it increases the rigidity of the entire Z-axis plate/lower plate structure, thereby improving its dynamic stiffness. Second, it serves as a rigid structure which may translate the upward/downward movement of the elevating screw 89 to the Z-axis plate 13 and keep the Z-axis plate 13 parallel to the lower plate 216. In a previously described embodiment, the elevating screw 89 is in contact with one of the guideposts 55 (as shown in
20 Figures 3A and 3B) so that the upward force of the elevating screw is translated through the guidepost to the Z-axis plate 13. However, the current design allows for additional stability since the spacer post 230 is rigidly affixed at both of its ends (as opposed to the previous design which rigidly affixed the guidepost at only one end). In a preferred embodiment, a single spacer post is used. In an alternate embodiment, a plurality of spacer posts may be
25 placed in between the Z-axis plate 13 and the lower plate 216.

In one embodiment, the elevating screw 89 is positioned at the center of gravity or center of effort of the stage. As discussed previously, the stage 27 typically is the portion of the microscope that provides movement of the sample. The stage 27 may move upward and downward during focusing and may include a plate, such as the dual plate which includes the
30 Z-axis plate 13 and the lower plate 216.

As discussed previously, the elevating screw 89 may have unwanted movement in the lateral direction. Because it is very difficult to make the elevating screw micron perfect (*i.e.*, eliminating the lateral movement in the elevating screw 89), the present design minimizes its

effects on the examination of the sample. The present design includes contacting the elevating screw with the lower plate rather than the Z-axis plate 13. Therefore, any lateral movement is felt by the lower plate 216 but not translated to the Z-axis plate 13. Specifically, because of the rigidity of the Z-axis plate/lower plate structure and because of the guideposts 55 and ball bushings 54, the lateral movement is not translated to the Z-axis plate 13 (upon which the sample sits and where focusing is performed). Thus, the current design allows for increased stability.

The lower plate 216 is "C" shaped and composed of the same material as the Z-axis plate 13. The shape of the lower plate 216 is dictated by the optical path in the microscope system. The light travels from the light source, through the open side portion of the "C" shaped lower plate 216, and reflected upward through the Z-axis plate 13. Moreover, as discussed previously, the guideposts 55 are affixed to the Z-axis plate 13 by an adhesive. In a preferred embodiment, the guideposts 55 are affixed to the lower plate 216 via collars 228. The collars 228, as shown in Figure 9C, have a guidepost opening 240, a slit 242 and screw openings 243. The collars 238 are affixed to the underside of the lower plate 216 by slipping the collars 228 through the guideposts 55 via the guidepost opening 240, placing a screw 244 through the slit 242 of the collars (to hold the collars securely to the guideposts 55), and placing screws 246 through the collar (to hold the collar to the underside of the lower plate 216).

Referring to Figure 10, there is shown an apparatus for providing upward and downward force. Similar to the elevating screw shown in Figures 2A and 3B, the apparatus includes a pulley which engages the top portion of a nut. The nut 87, via a collar 250, is in contact with the inner race of radial bearings 57. The outer race of the radial bearings 57 is in contact with the base 12 (so that the outer race does not move). The nut 87 contacts the elevating screw 89 via ball bearings 248. During operation, the pulley 61 exerts force on the nut 87 thereby turning the nut 87. Because of the radial ball bearings 57, the nut 87 does not move upward/downward. The radial movement of the nut 87 is translated into an upward/downward movement of the elevating screw 89. For additional stability, thrust bearings 252 are added at the lower portion of the apparatus. The inner portion of the thrust bearings 252 is in contact with the collar 250 and the outer portion is in contact with the base 12 (so that the outer portion does not move). The thrust bearings 252 complement the column design of the z-axis elevating screw drive, making the drive less compressible and stabilizing the drive in the thrust direction. Thus, through the use of the radial bearings 57

and the thrust bearings 252, the nut is more secure during movement, so that the elevating screw is likewise more secure.

Rotating Wheel

As described above, the microscope system includes a lamp for illuminating the sample. Specific frequencies of illumination are desired depending on the operation of the microscope. In order to filter out the unwanted frequencies, a motorized rotating filter wheel mechanism 254 is designed into the microscope frame. This mechanism 254 is located in the illumination system path just after the lamp collector lens and heat shield system, as shown in Figure 11A. It is positioned before the field iris diaphragm. Locating the filter mechanism in this location has the following benefit of illuminating the specimen with only the specific wavelength light desired and not the broad spectrum. This has certain advantages in some forms of the quantifiable imaging systems. An additional benefit is the reduction in the amount of vibrations. Because the filter mechanism uses a motor as the prime mover, the vibrations caused by the motor and the moving mass do not have a negative effect on the stability of the camera system. Because the motorized rotating filter wheel is (1) located far from the camera (relative to other components in the microscope) and (2) in the base component, the most stable component of the system, so that the wheel does not appreciably affect the operation of the camera. In one embodiment, the rotating wheel has 6 slots 256, as shown in Figure 11B. The wheel 254 rotates so that filters placed in the slots 256 modify the spectrum of light in the optical path.

In one embodiment, the rotating wheel rotates at hundreds of revolutions per minute. The wheel is in communication with camera 127, sending information regarding the slot (and in turn the filter) that is positioned before the field iris diaphragm. In an exemplary embodiment, the rotating wheel has 6 slots so that when a particular slot is before the field iris diaphragm, a message (e.g., a specific bitstream) is sent to the camera 127. Thus, in a single rotation of the wheel, six messages are sent to the camera 127, indicating at the appropriate time that slots 1 through 6 are before the field iris diaphragm. The camera 127 receives instructions from processor (e.g., processor 105) telling the camera 127 which of the six filters to choose. For example, if slot 2 is the filter desired, when the rotating wheel sends the instruction that slot 2 is before the field iris diaphragm, the camera 127 instructs the frame grabber to select the image received. As one example, images at two specific wavelengths are analyzed, with one image around 520 nm and the other image around 630 nm. In order to obtain an image of the samples at these specific wavelengths, narrow band filters centered

around the specific wavelengths are put into two of the slots (*e.g.*, filter passes wavelengths between 515 nm to 525 nm). When one of the filters is in position, a specific bitstream is sent to camera 127. The camera then grabs the image.

Monochromatic cameras are typically more accurate than color cameras; however, a color image may assist in cytological analysis. Therefore, after the images for the respective wavelengths is analyzed, a color image may be generated using wide band red, green and blue filters that are placed in the slots 256. Similar to the operation described above, when a specific filter is in place, a message is sent to the camera to capture the image. After the image for the red, blue and green filters are captured, a color image is created.

An exemplary embodiment of the present invention has been described herein. It is to be understood, of course, that changes and modifications may be made in the embodiment without departing from the true scope and spirit of the present invention, as defined by the appended claims.

CLAIMS

I claim:

1. A microscope system comprising, in combination:

a base portion extending from a front end to a back end;

an upper portion extending from a front end to a back end;

a back support extending from the back end of the base portion to the back end of the upper portion and providing rigid support of the back end of the upper portion in relation to the back end of the base portion;

a stage for supporting a specimen, the stage being movable in relation to the base portion, the upper portion and the back support;

a brace rigidly connecting the front end of the base portion to the front end of the upper portion; and

an optical element mounted on the upper portion between the back support and the brace.

2. The microscope system of claim 1, wherein the stage has an outermost position, and

wherein the bridge includes a lower portion connected to the front end of the base portion and an upper portion connected to the front end of the upper portion, the lower portion and the upper portion meeting at a surface with an innermost point, the innermost point of the surface being adjacent to the stage at its outermost position.

3. The microscope system of claim 1, wherein the bridge includes a lower portion connected to the front end of the base portion and an upper portion connected to the front end of the upper portion, the lower portion and the upper portion meeting at a surface with an innermost point, an angle measured at the innermost point being less than 180°.

4. The microscope system of claim 3, wherein the angle measured at the innermost point is between 90° and 180°.

5. The microscope system of claim 1, wherein a cross-section of the brace is a "T" shape.

6. In a microscope comprising a base portion having a back end, an upper portion having a back end, a back support connected to the back end of the base portion and to the back end of the upper portion and providing rigid support of the back end of the upper portion in relation to the back end of the base portion, a stage for supporting a specimen, the stage being movable in relation to the base portion, the upper portion and the back support,

and an optical element mounted on the upper portion between the back support and the brace, the improvement comprising, in combination:

a brace rigidly connecting the base portion to the upper portion, the brace connected to the base portion at a point other than the back end of the base portion, the brace connected to the upper portion at a point other than the back end of the upper portion.

7. The microscope system of claim 6, wherein the base portion includes a front end and the upper portion includes a front end, the brace connected to the front end of the base portion and the front end of the upper portion.

8. The microscope system of claim 7, wherein the bridge includes a lower portion connected to the front end of the base portion and an upper portion connected to the front end of the upper portion, the lower portion and the upper portion meeting at a surface with an innermost point, an angle measured at the innermost point being less than 180° .

9. The microscope system of claim 8, wherein the angle measured at the innermost point is between 90° and 180° .

10. The microscope system of claim 6, wherein a cross-section of the brace is a "T" shape.

11. A microscope system comprising, in combination:

a base;

a first plate, the first plate upon which a sample is placed;

a second plate;

at least one spacer post, the spacer post connected to the first plate and the second plate;

means for moving the second plate upward or downward, the means for moving the second plate upward and downward in contact with the second plate;

a light source for generating light to irradiate the sample;

a magnifier for creating a magnified image of the sample;

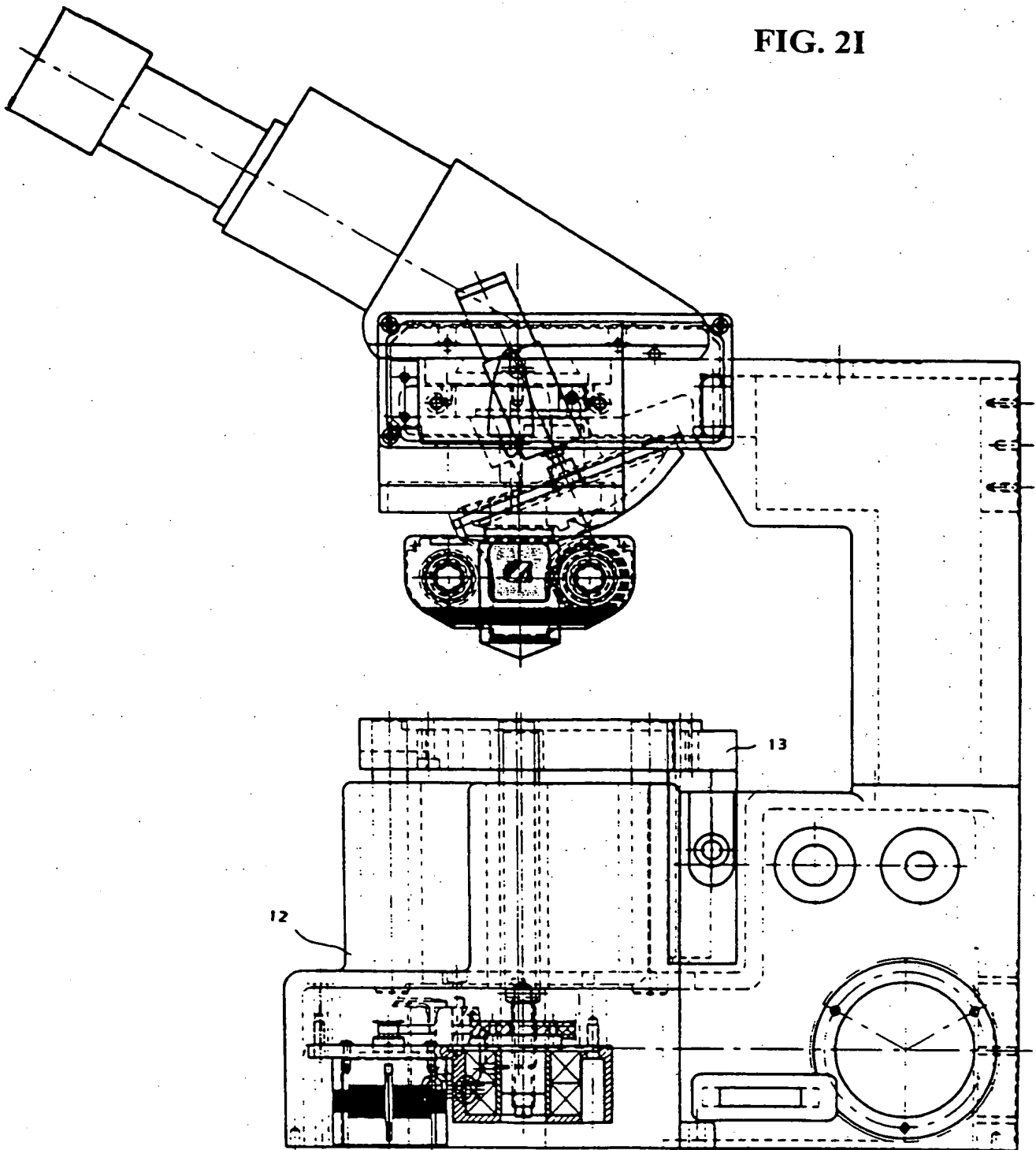
a viewer for receiving the magnified image of the sample; and

an optical path defined cooperatively by said first plate, said second plate, said light source, said magnifier and said viewer.

12. The microscope system of claim 11, further comprising at least two guideposts, the two guideposts rigidly fixed to the first plate and the second plate.

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FIG. 2I



13. The microscope system of claim 12, further comprising at least two bushings, the bushings affixed to the base, the bushings running in an interference mode with the guideposts.

14. The microscope system of claim 13, wherein the bushings are placed directly
5 below the first plate.

15. The microscope system of claim 13, wherein the bushings are placed directly above the second plate.

16. The microscope system of claim 11, wherein the means for moving the second plate upward and downward includes an elevating screw.

10 17. The microscope system of claim 16, wherein the spacer post is positioned directly above the elevating screw.

18. A microscope system comprising, in combination:

a light source for generating light to irradiate the sample;

a magnifier for creating a magnified image of the sample;

15 a rotating wheel having a plurality of filters, the filters passing certain wavelengths of light;

a motor for rotating the rotating wheel at a constant speed;

an imaging system having a viewer, the imaging system for obtaining the magnified image from the viewer and producing an electronic image; and

20 an optical path defined cooperatively by the light source, the magnifier and said viewer,

wherein a portion of the rotating wheel is in the optical path,

wherein the rotating wheel in communication with the imaging system,

25 wherein the rotating wheel indicates to the imaging system which filter is in the optical path, and

wherein the imaging system determines when to capture an image in the optical path based on the indication by the rotating wheel of which filter is in the optical path.

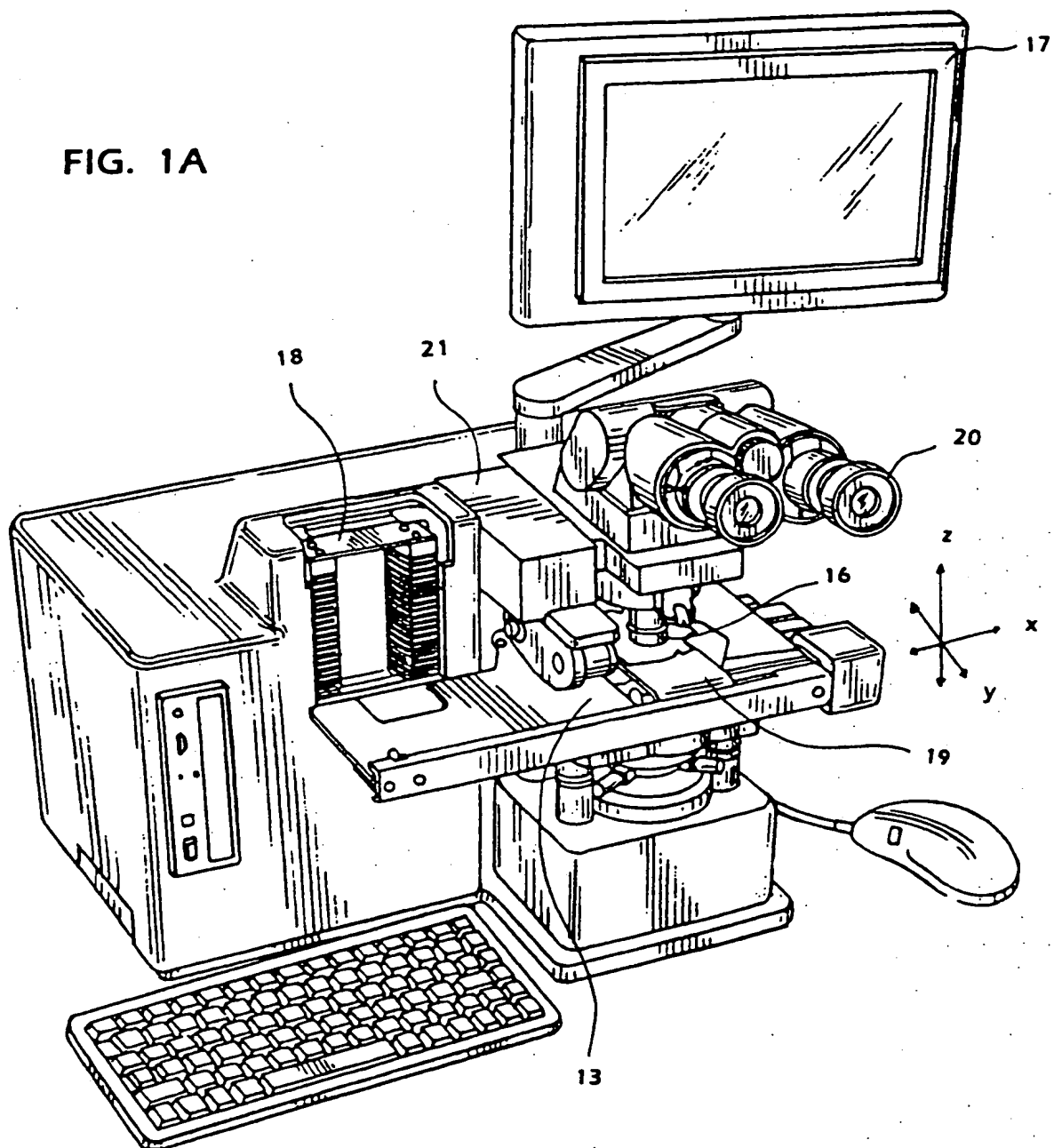
19. The microscope system of claim 18, wherein the imaging system is a camera.

20. The microscope system of claim 18, wherein the magnifier includes a field iris
30 diaphragm, and

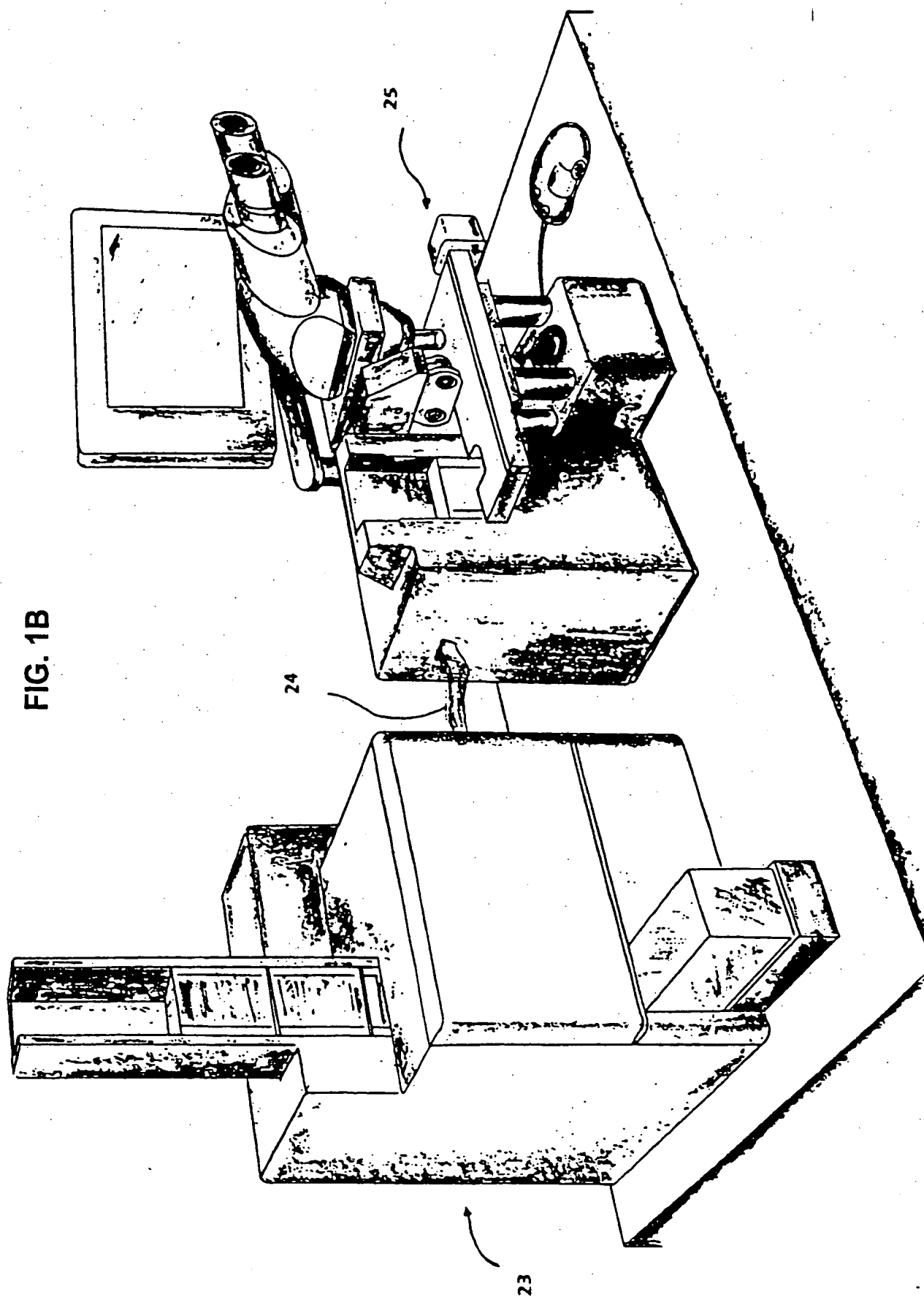
wherein the rotating wheel is position in the optical path before the field iris diaphragm.

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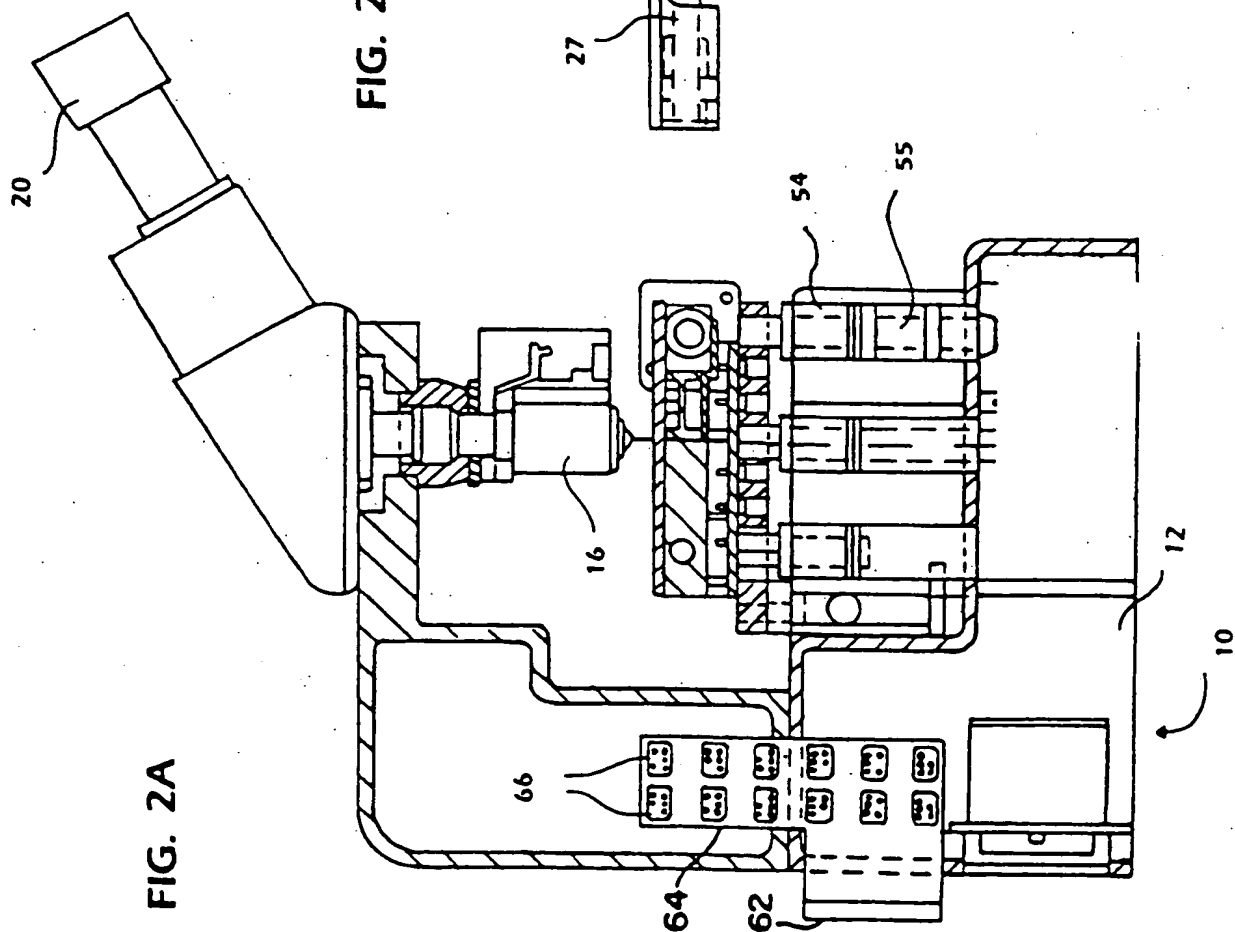
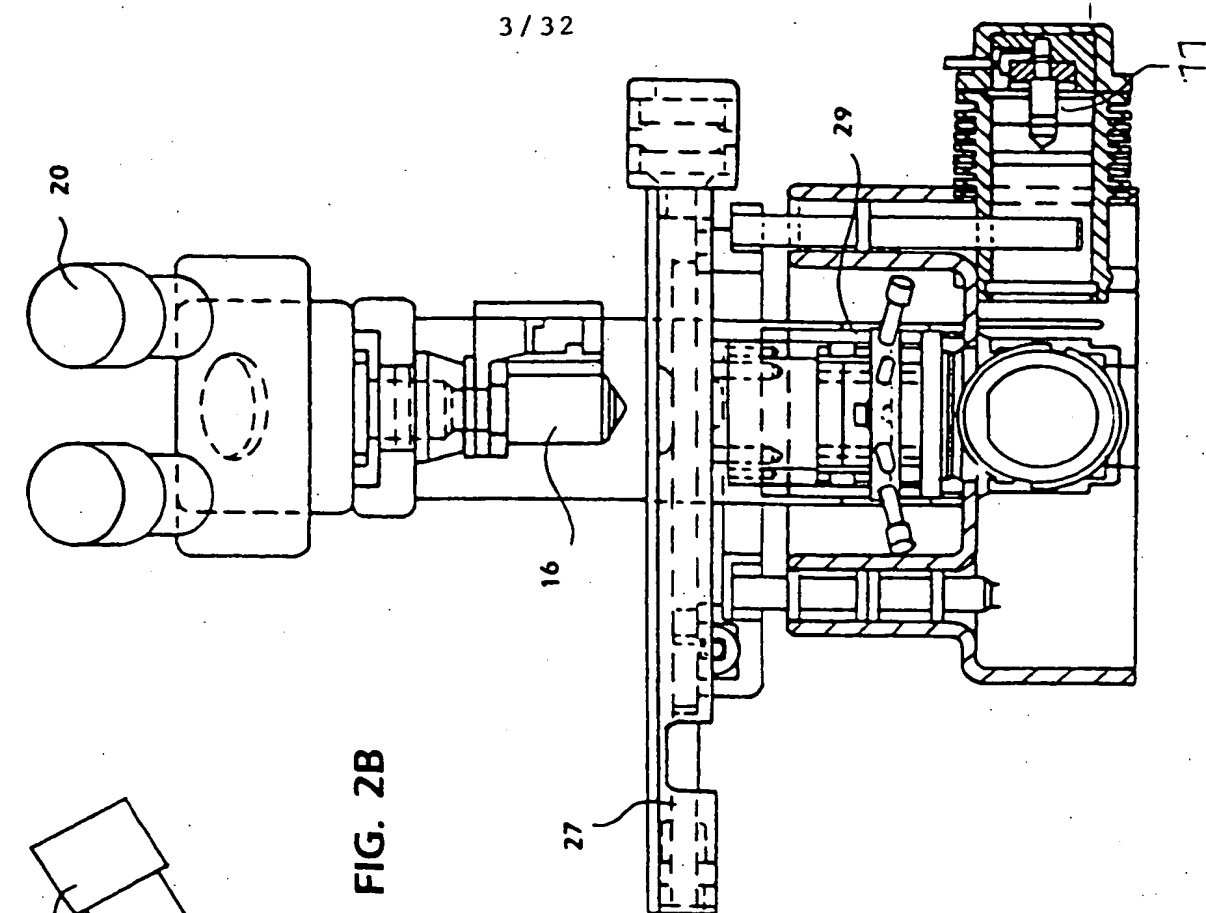
FIG. 1A



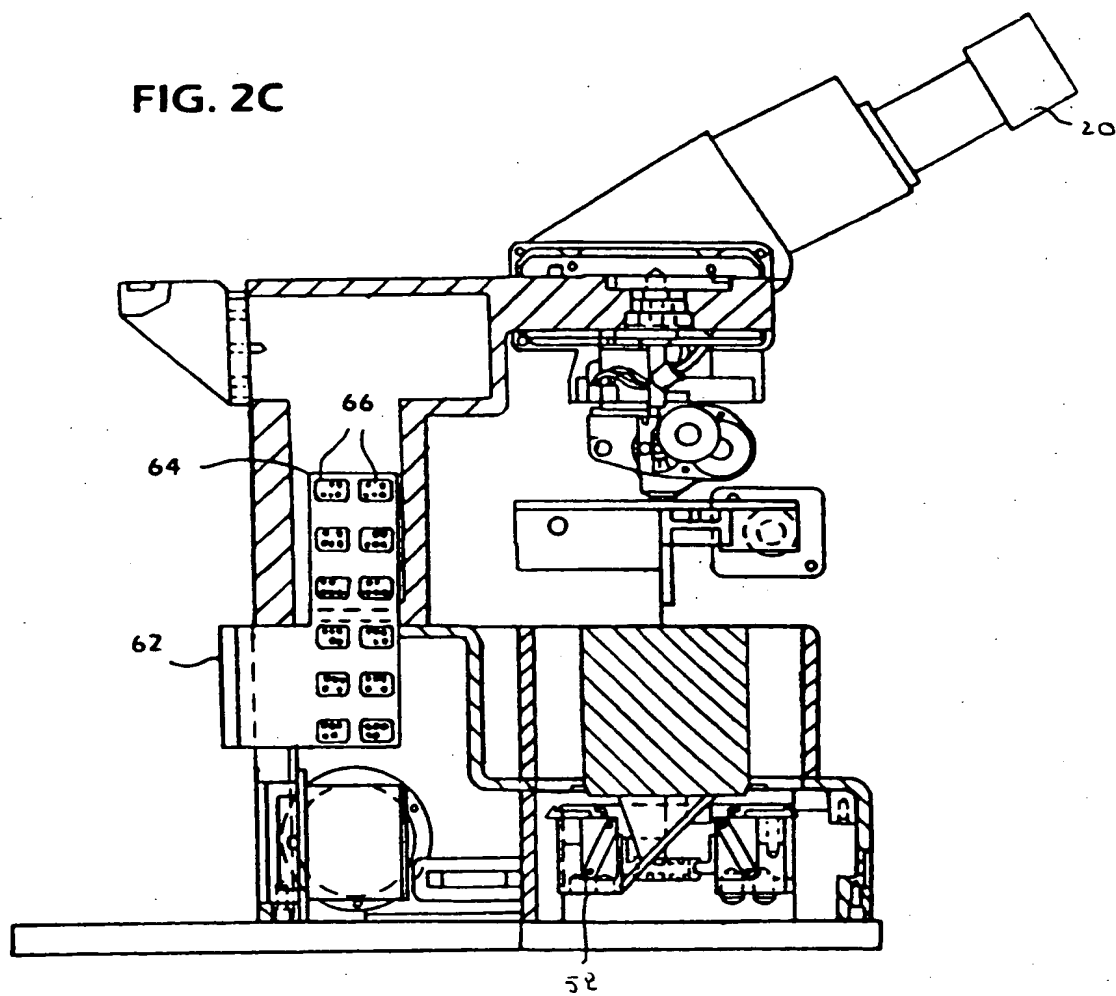
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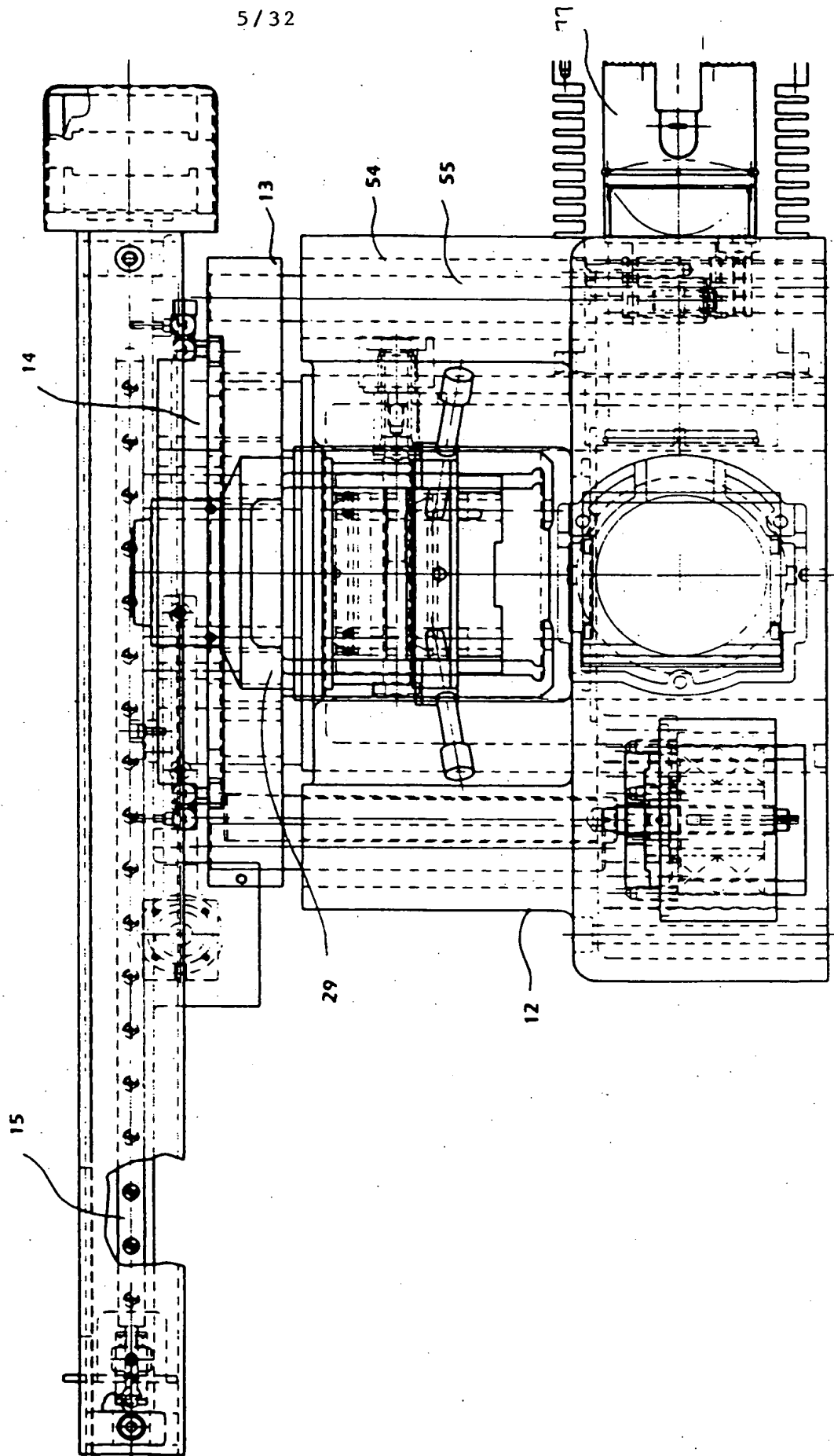


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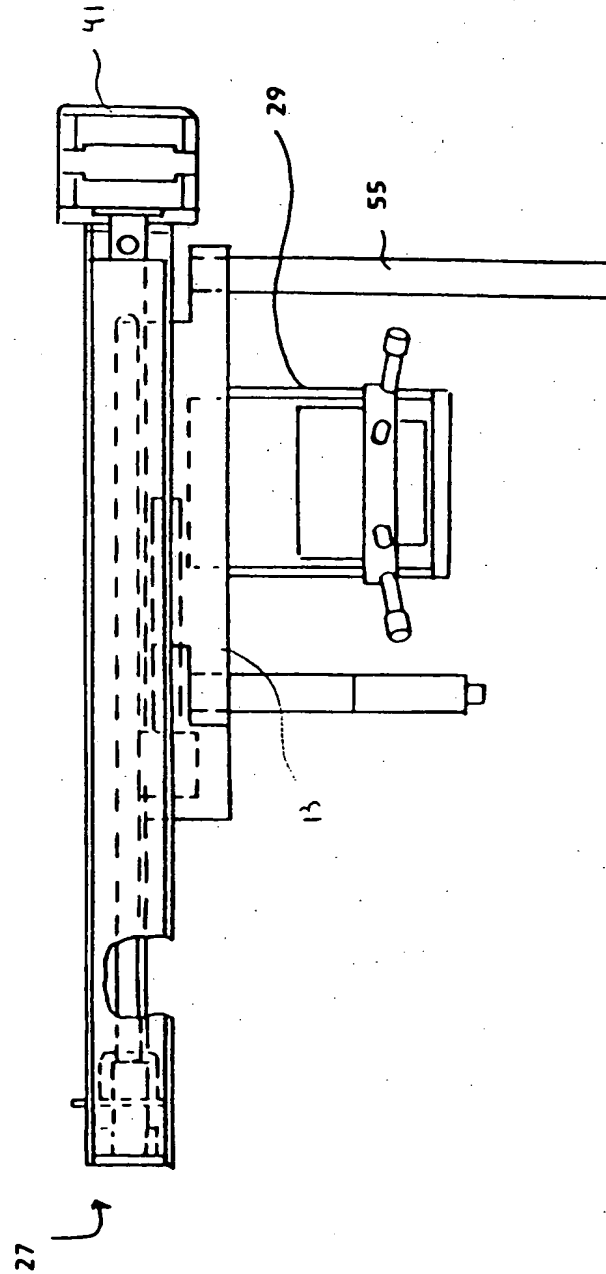
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FIG. 2D



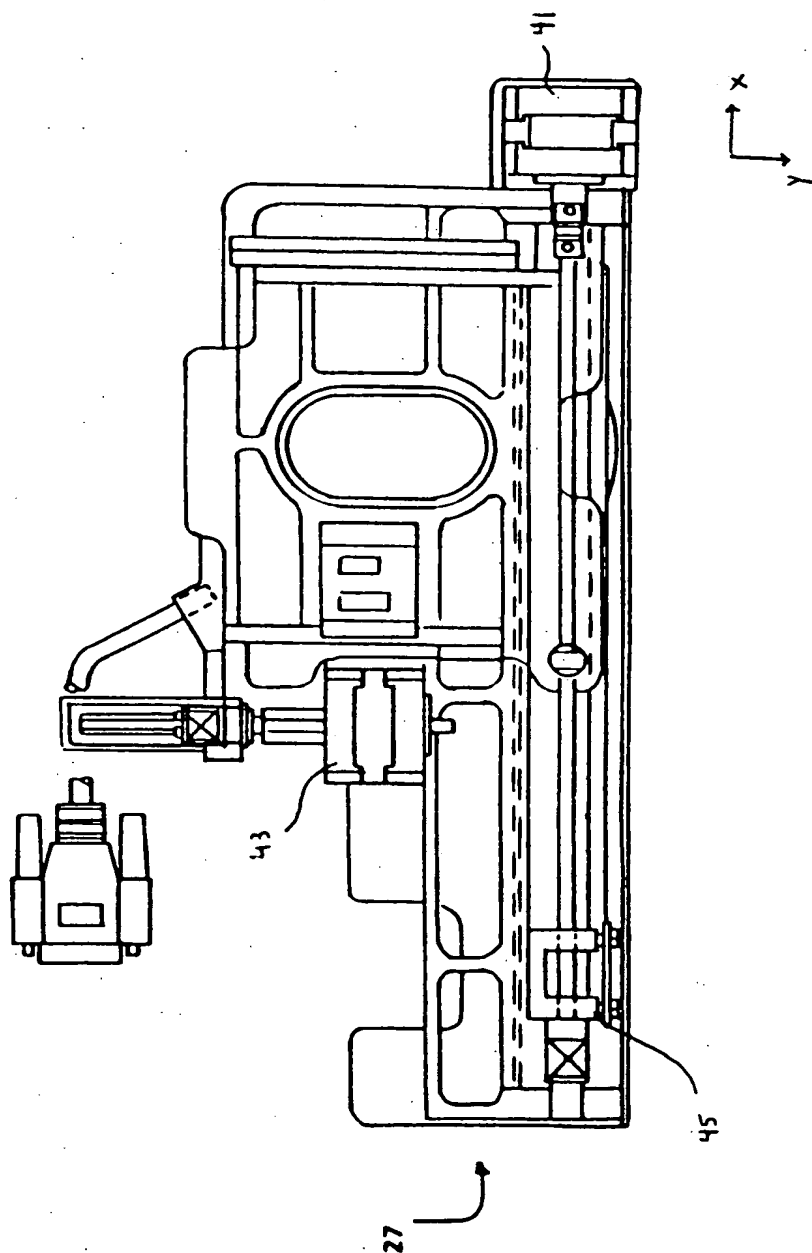
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FIG. 2E



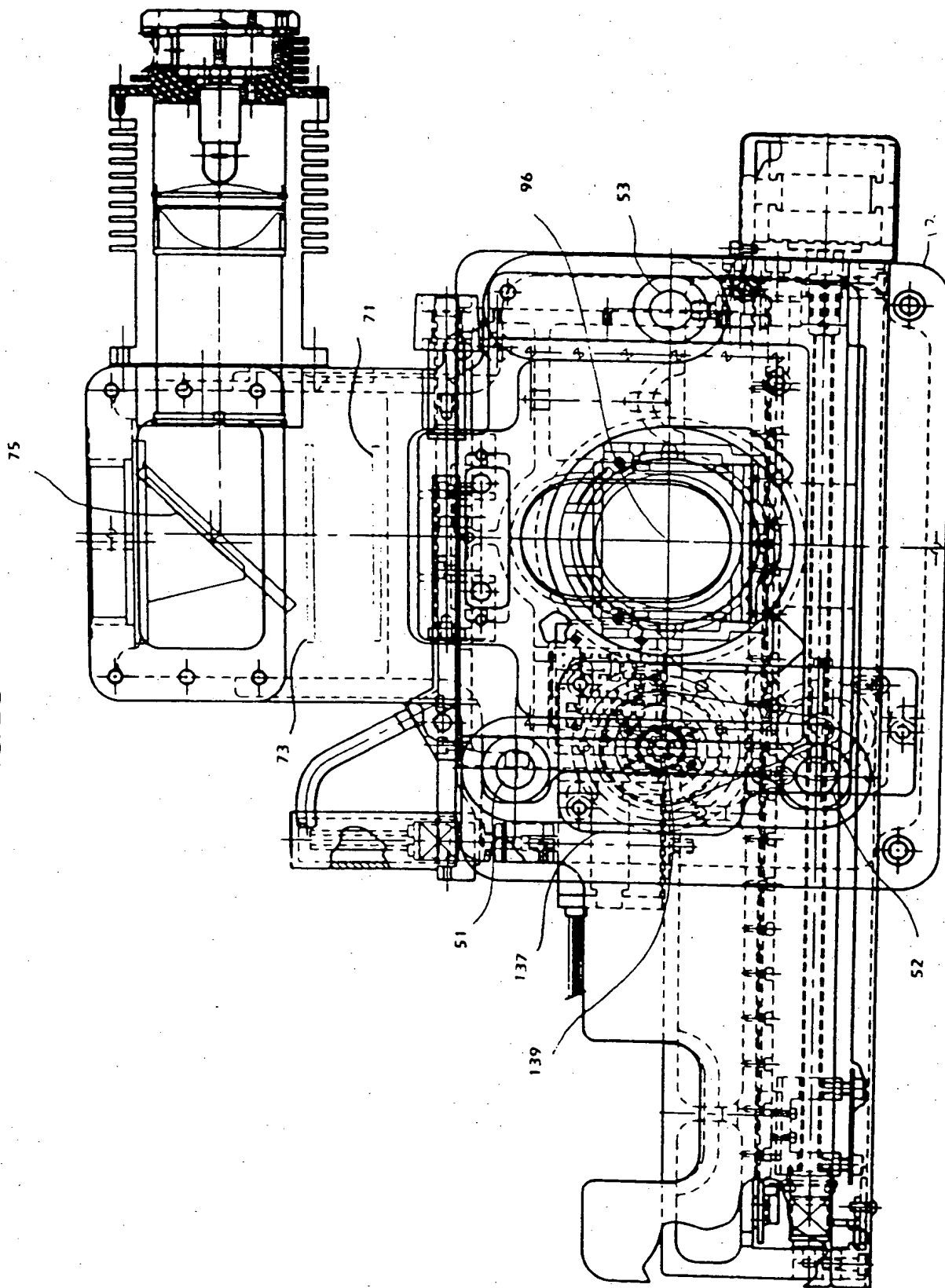
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FIG. 2F



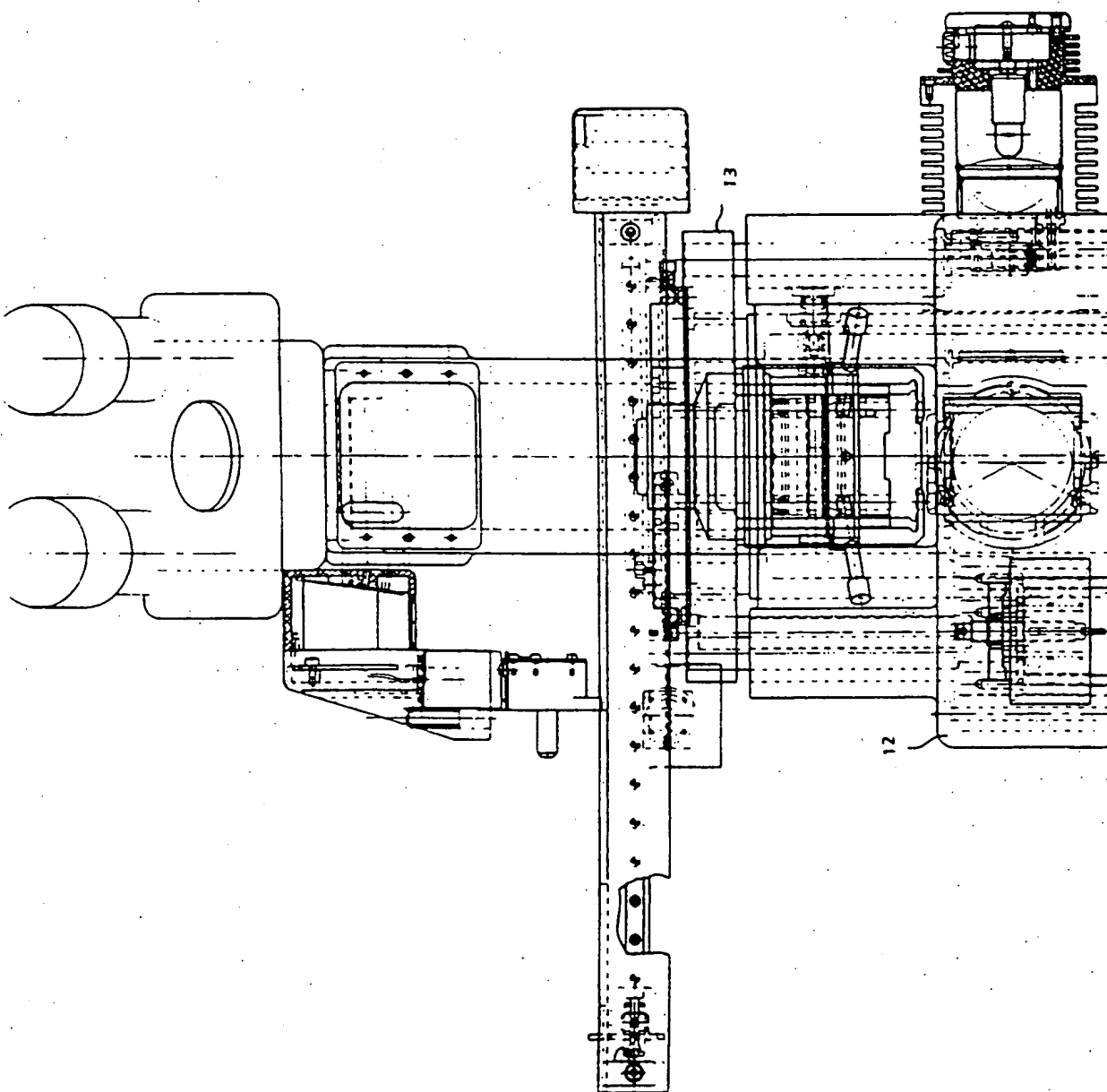
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FIG. 2G



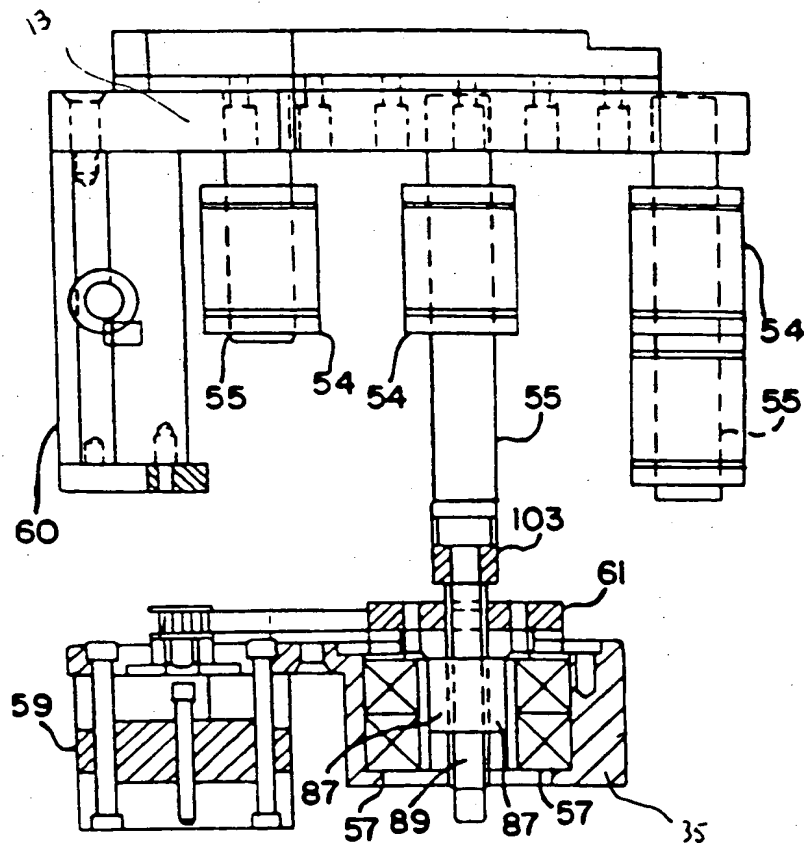
9/32

FIG. 2H



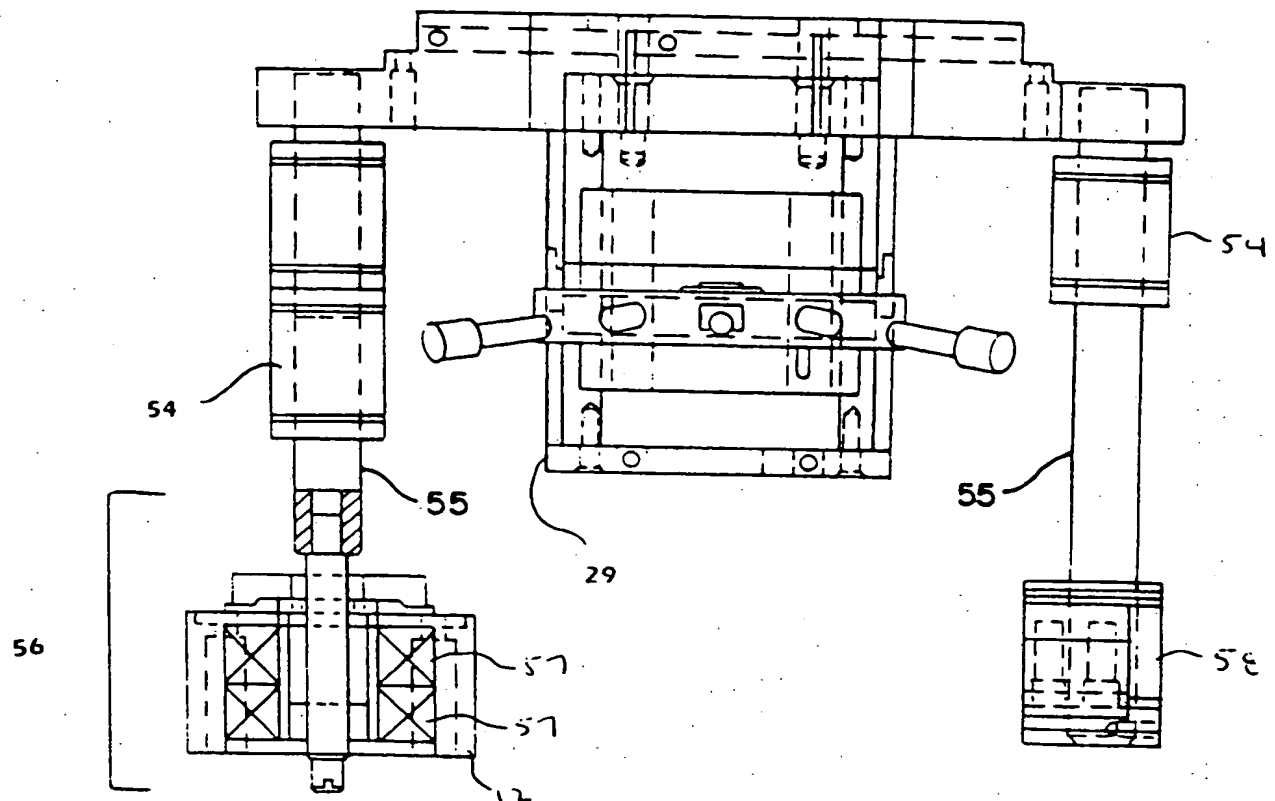
11/32

FIG. 3A



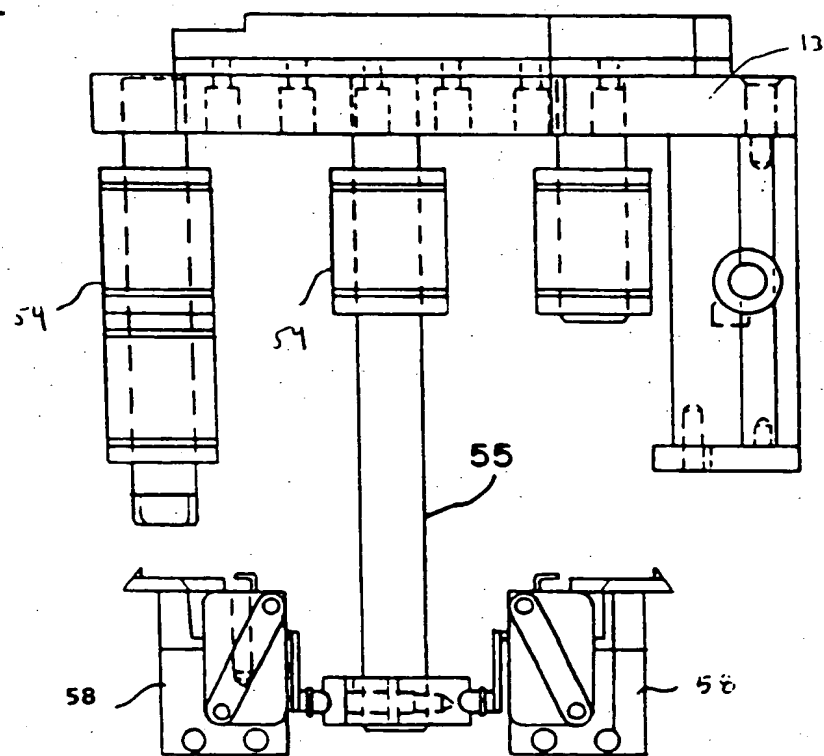
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FIG. 3B



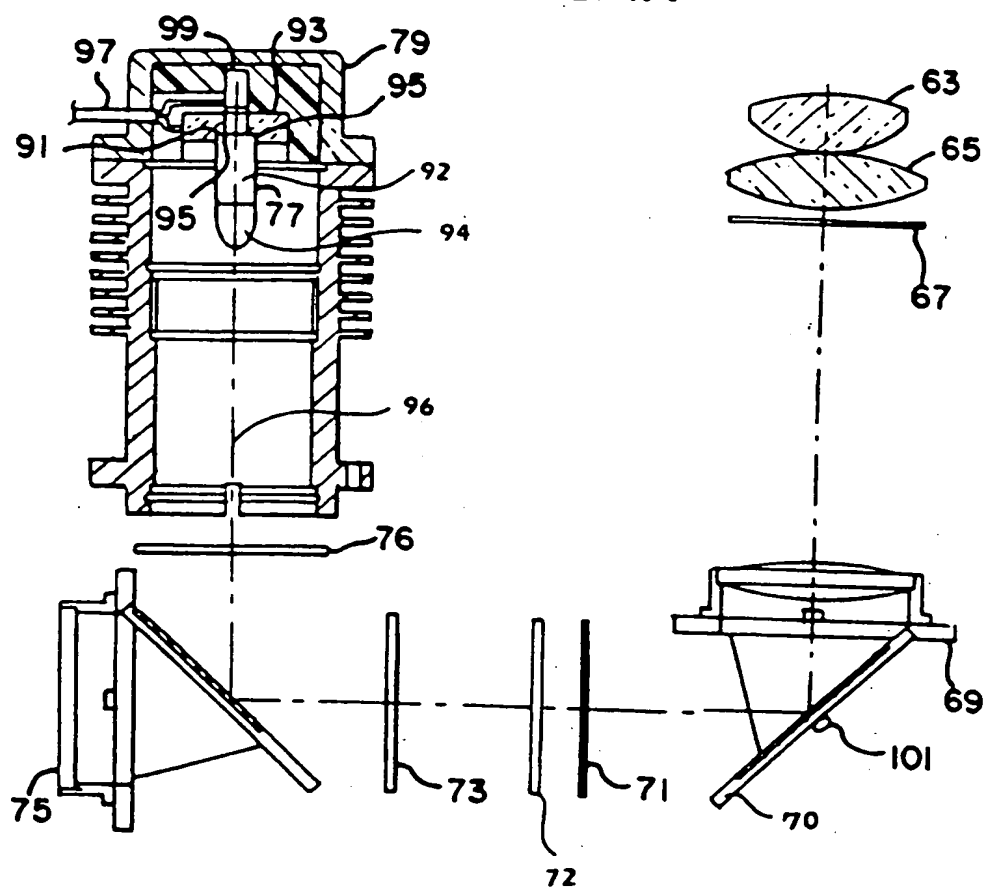
13/32

FIG. 3C



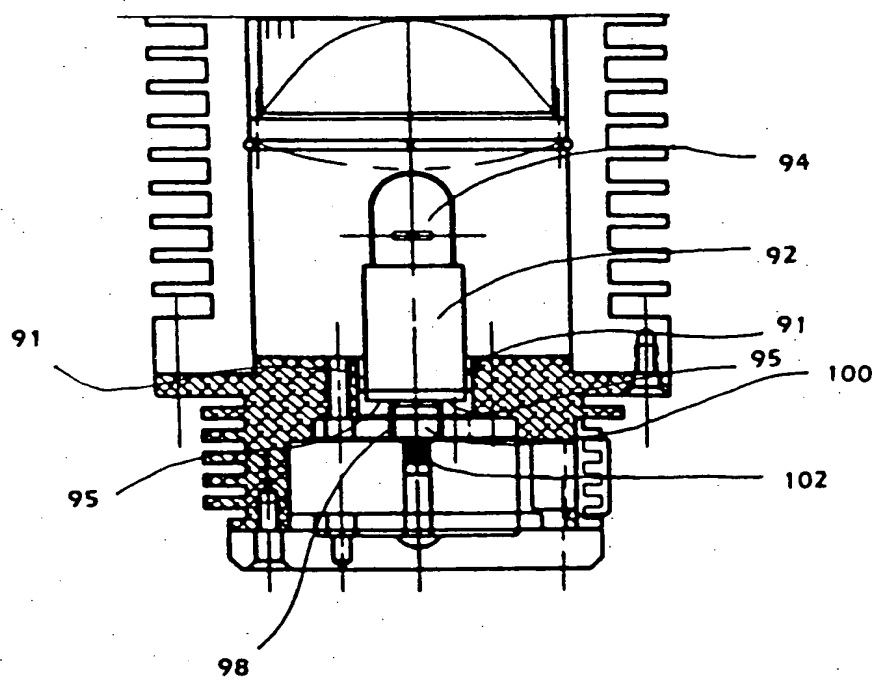
14/32

FIG. 4A



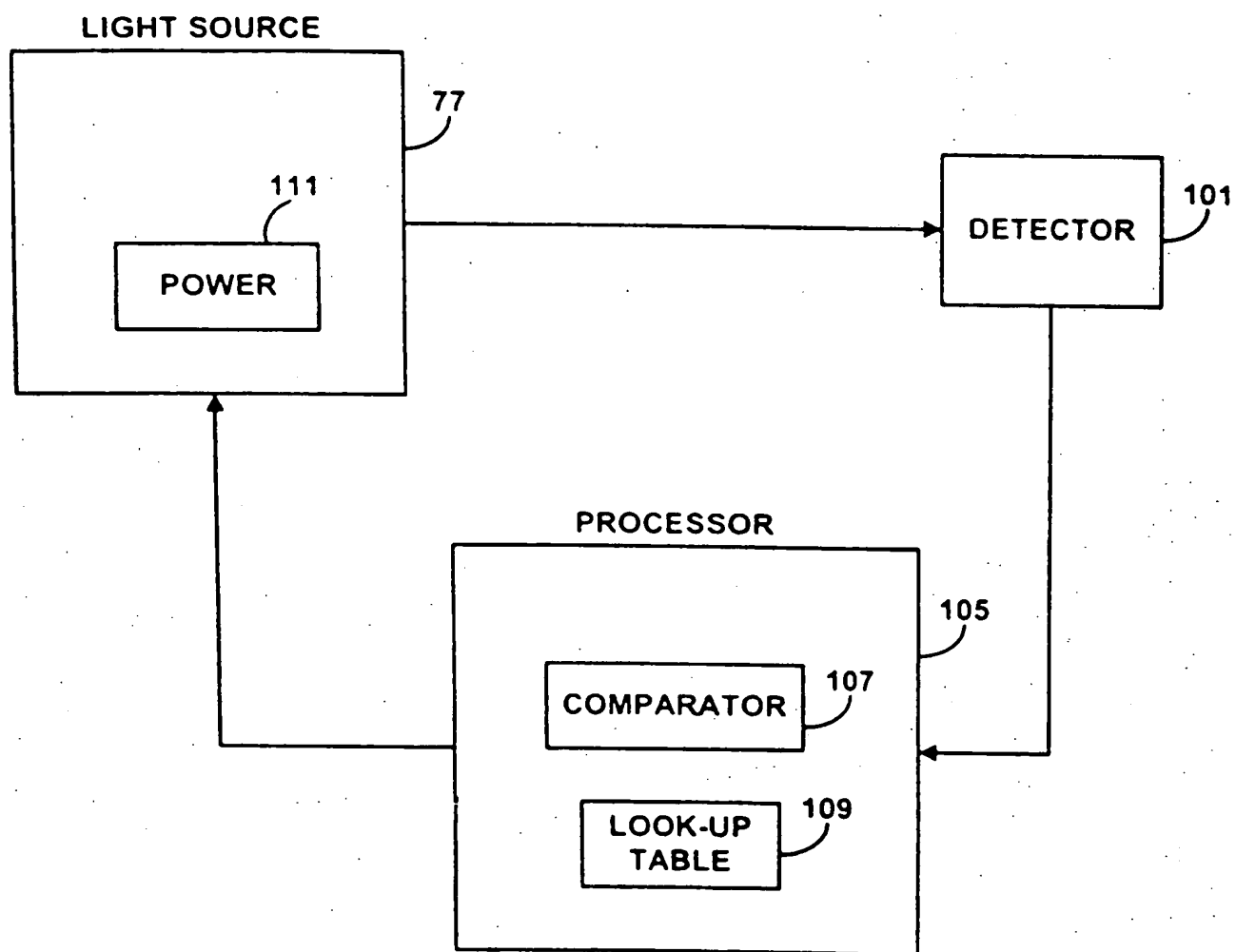
15/32

FIG. 4B



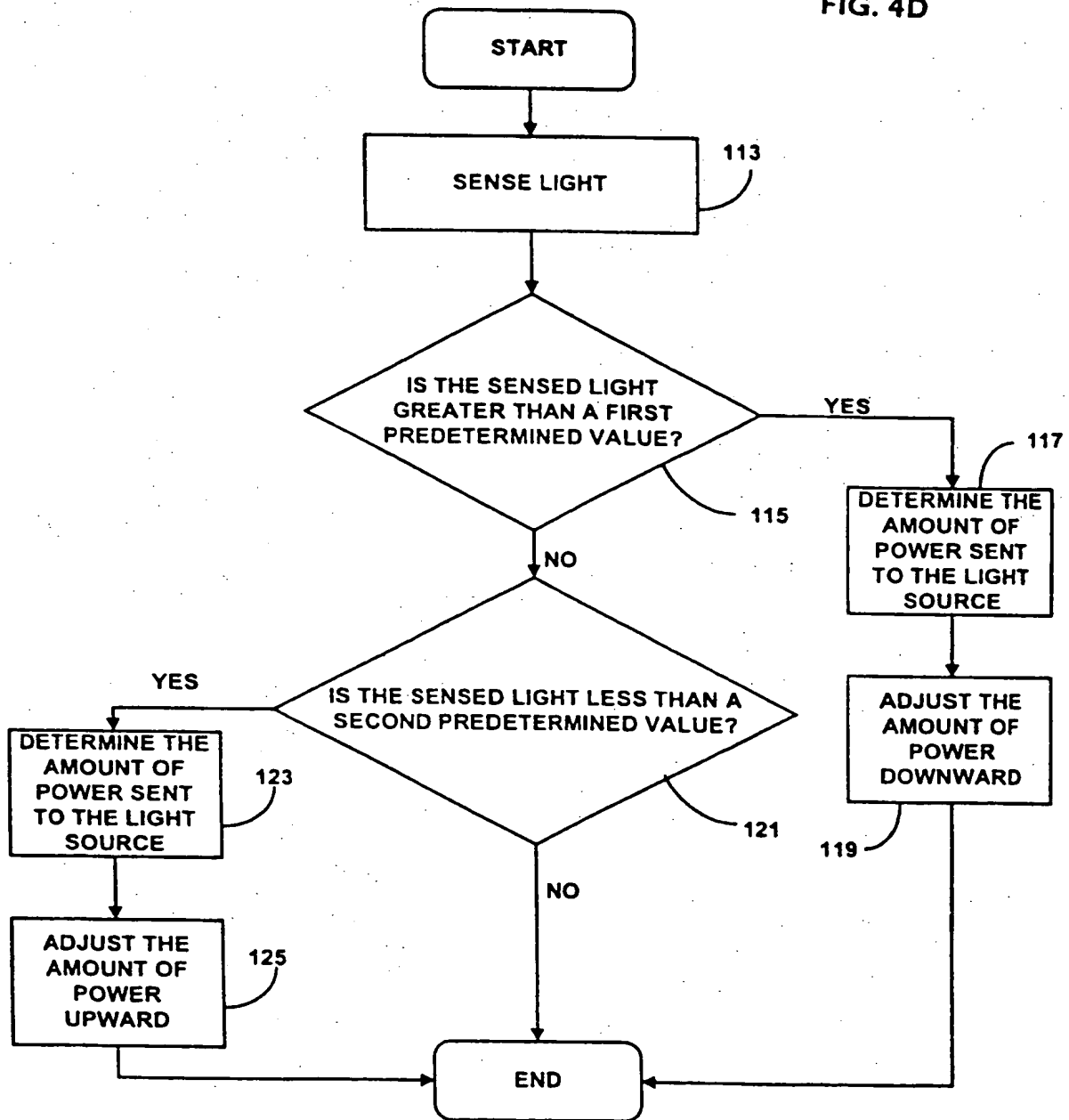
16/32

FIG. 4C



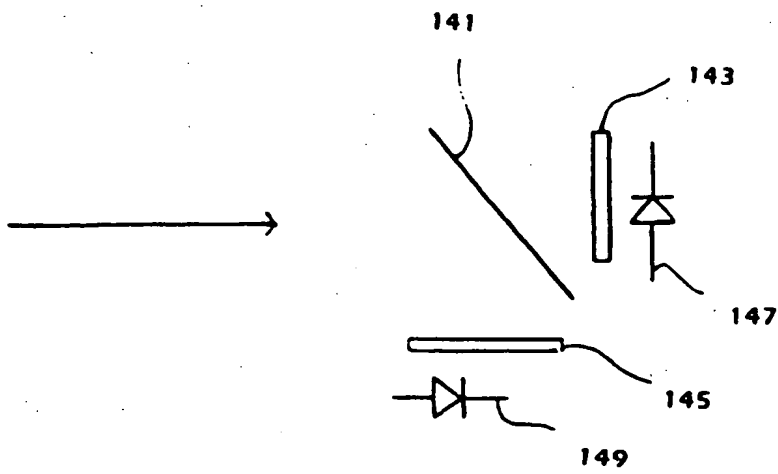
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FIG. 4D



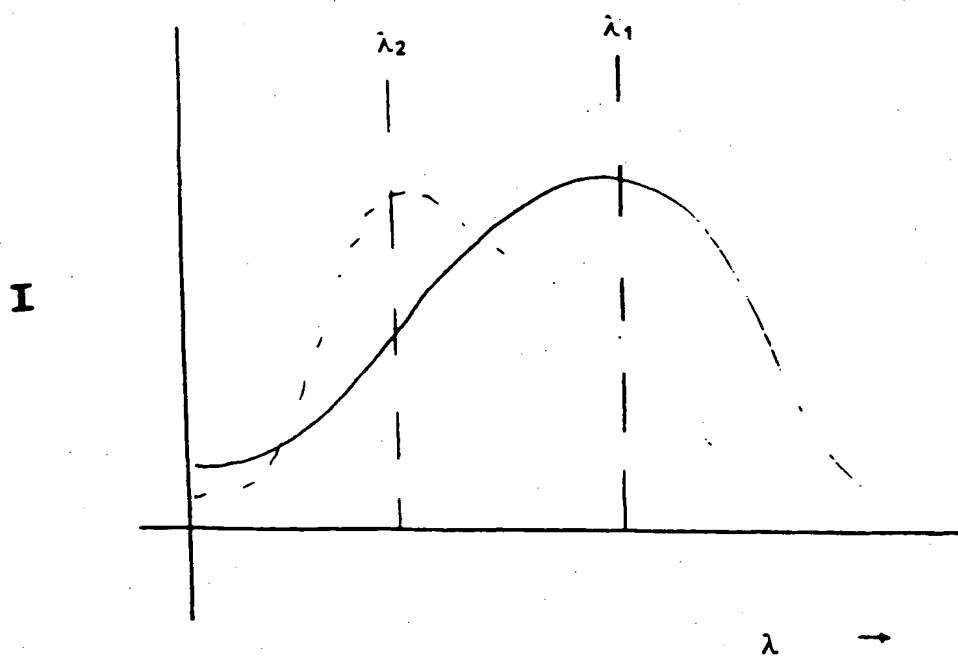
18/32

FIG. 4E



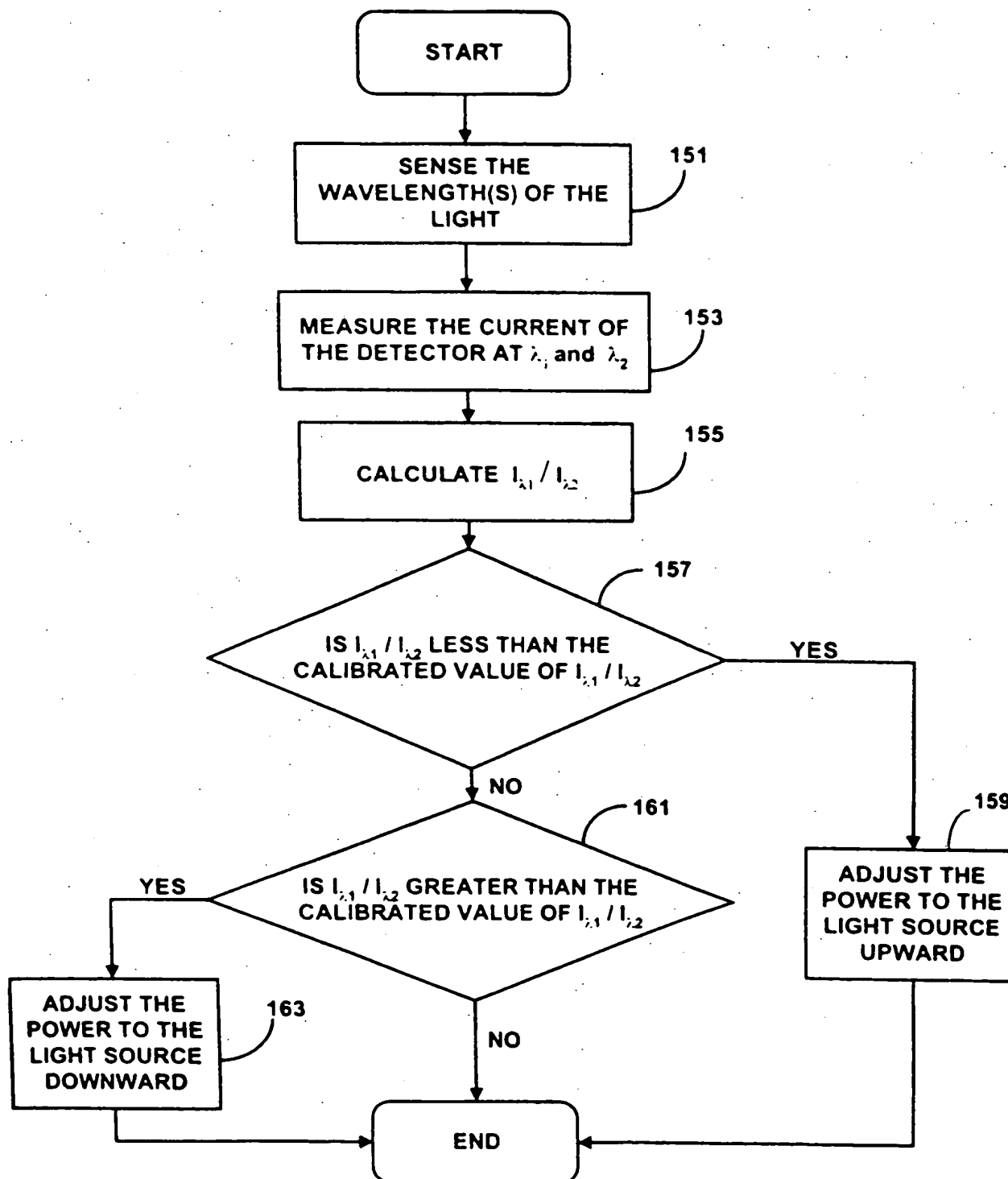
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FIG. 4F



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FIG. 4G



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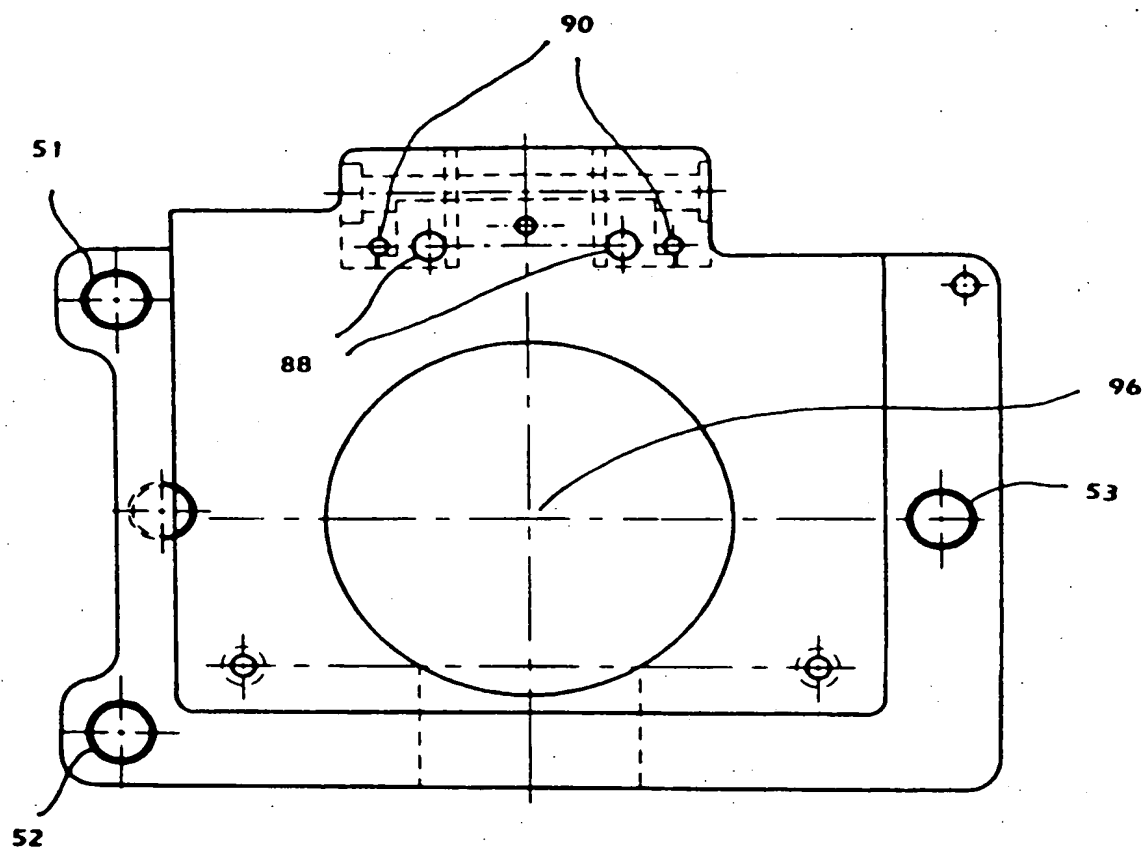


FIG. 5B

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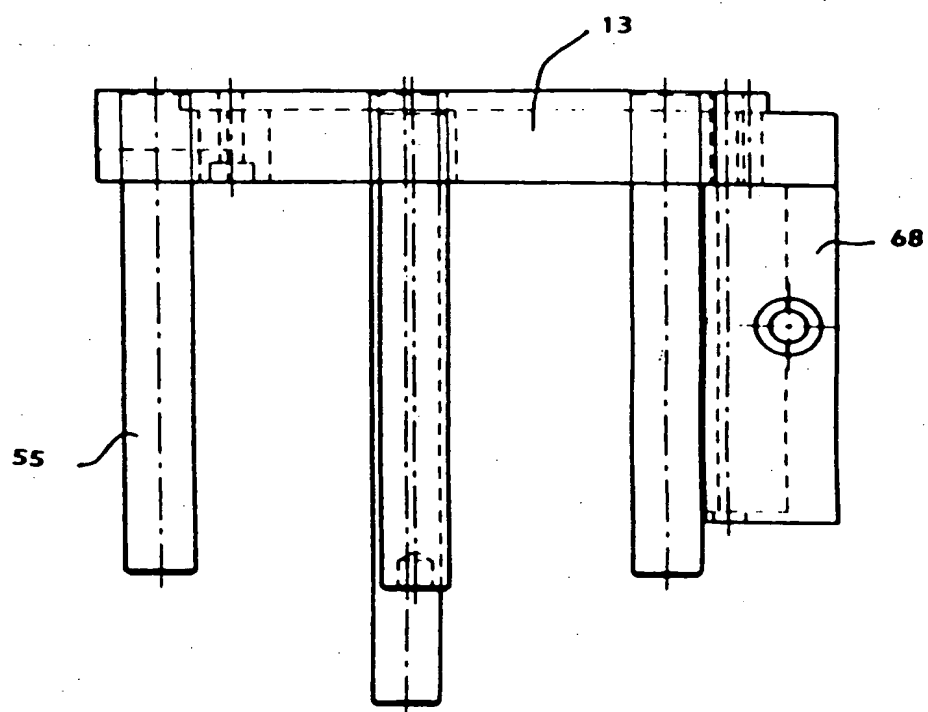
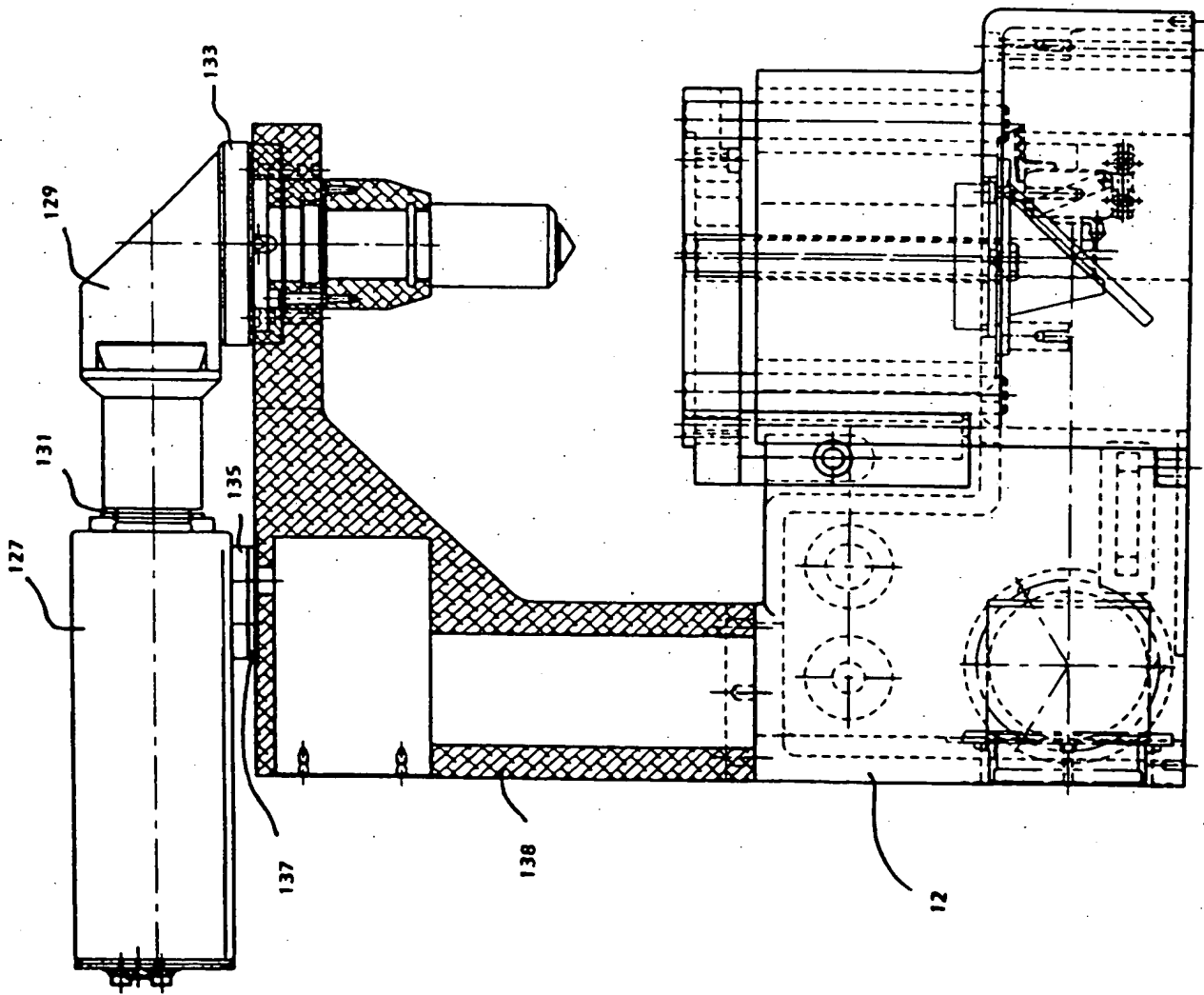


FIG. 5C

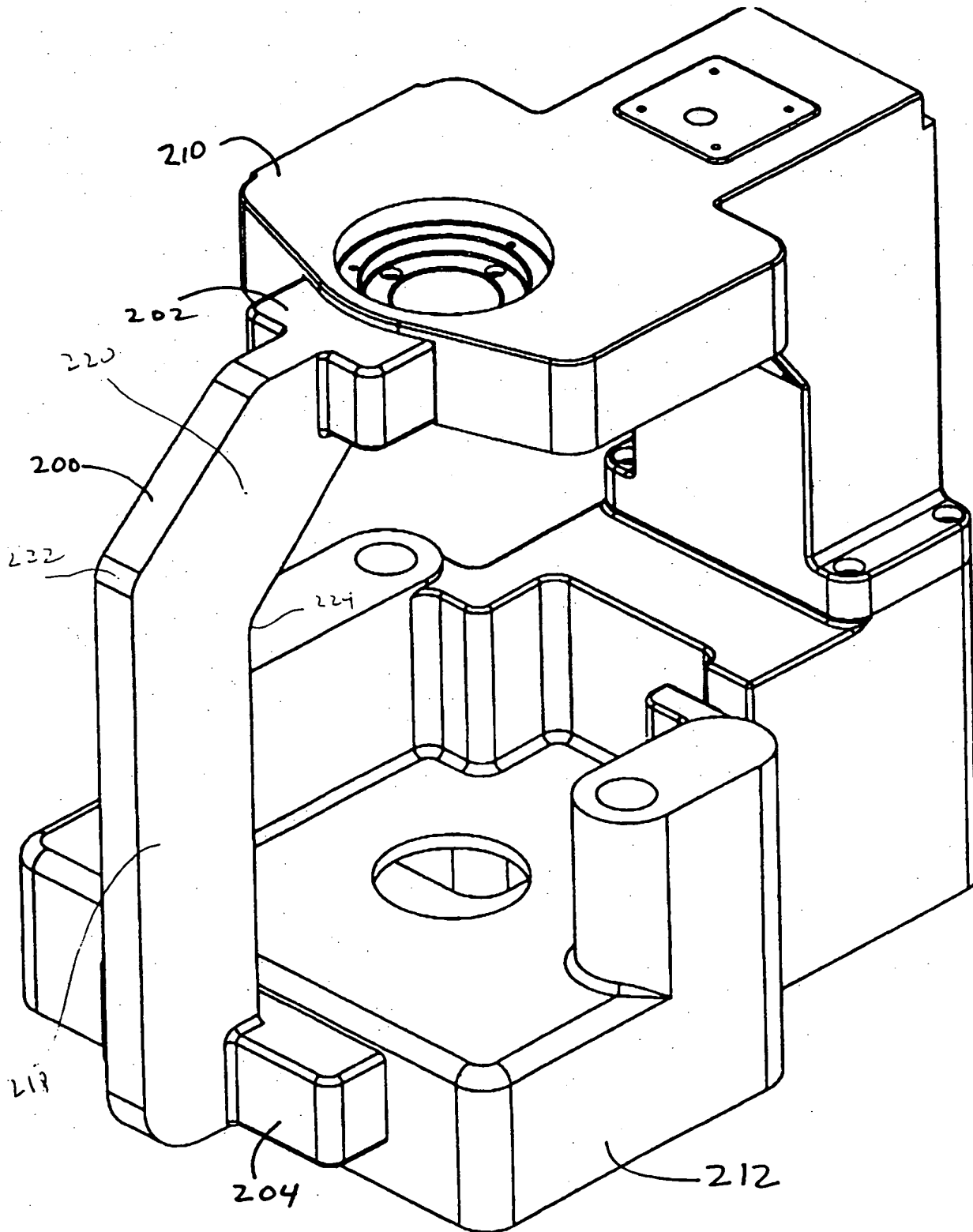
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FIG. 6



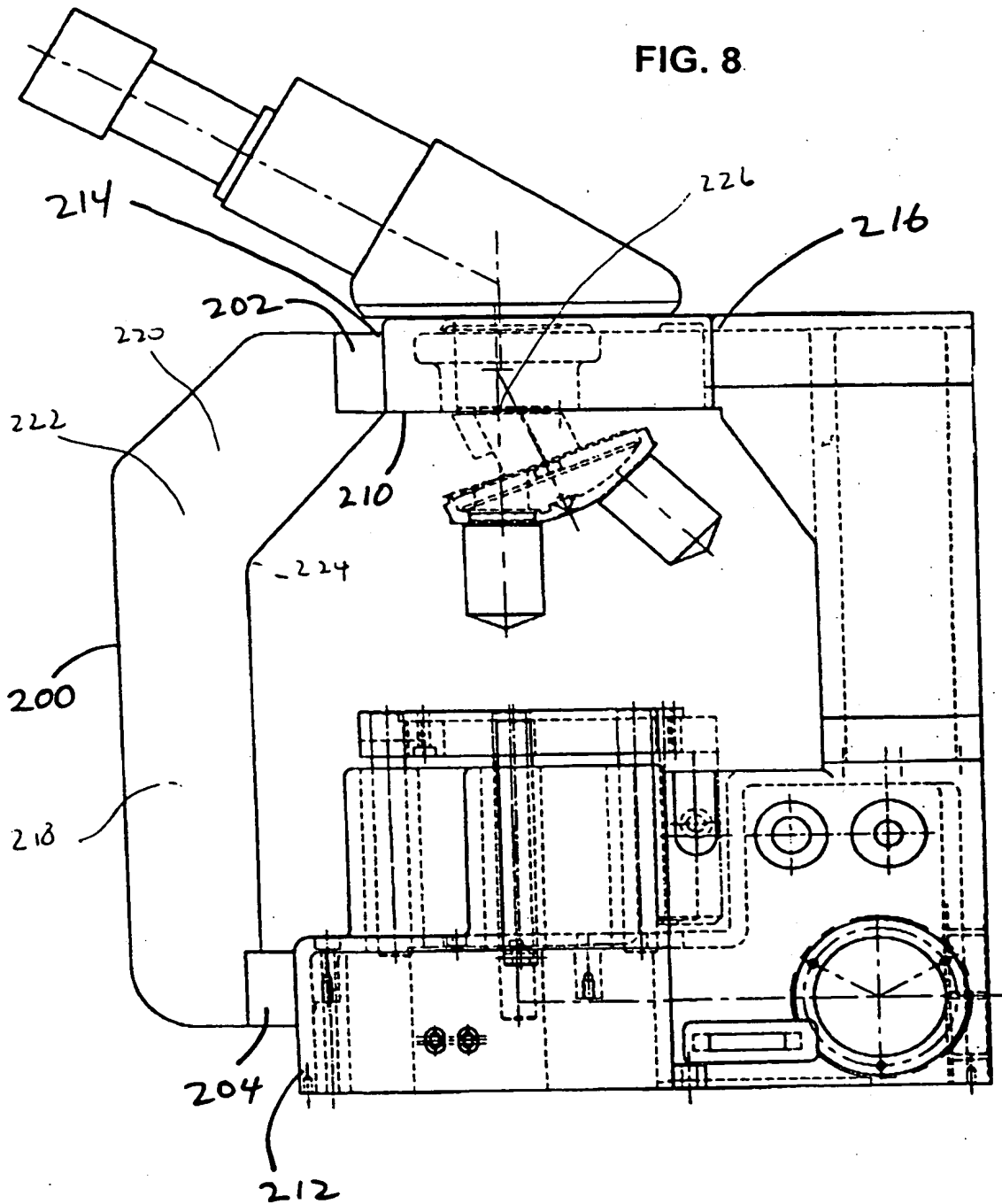
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FIG. 7



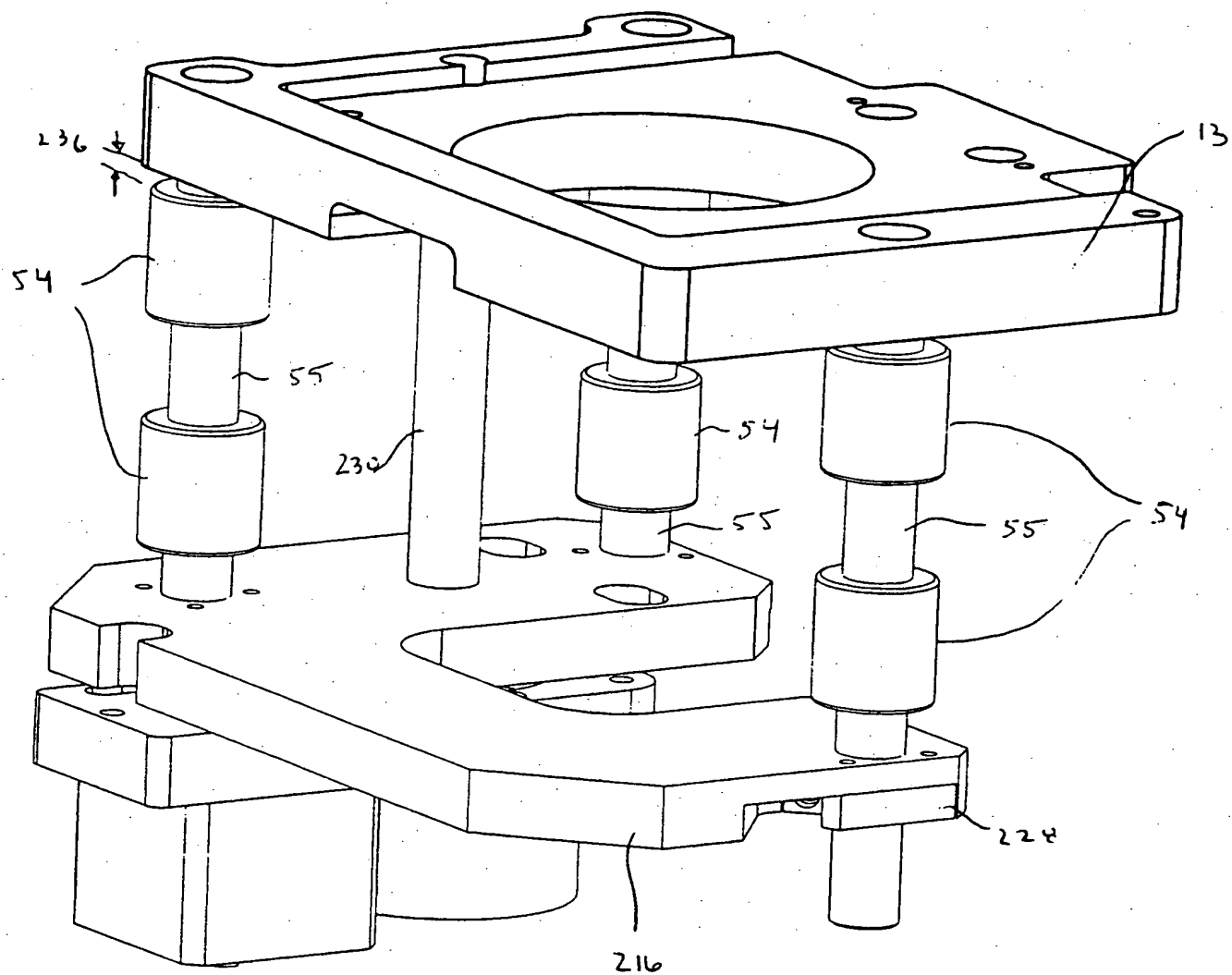
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FIG. 8



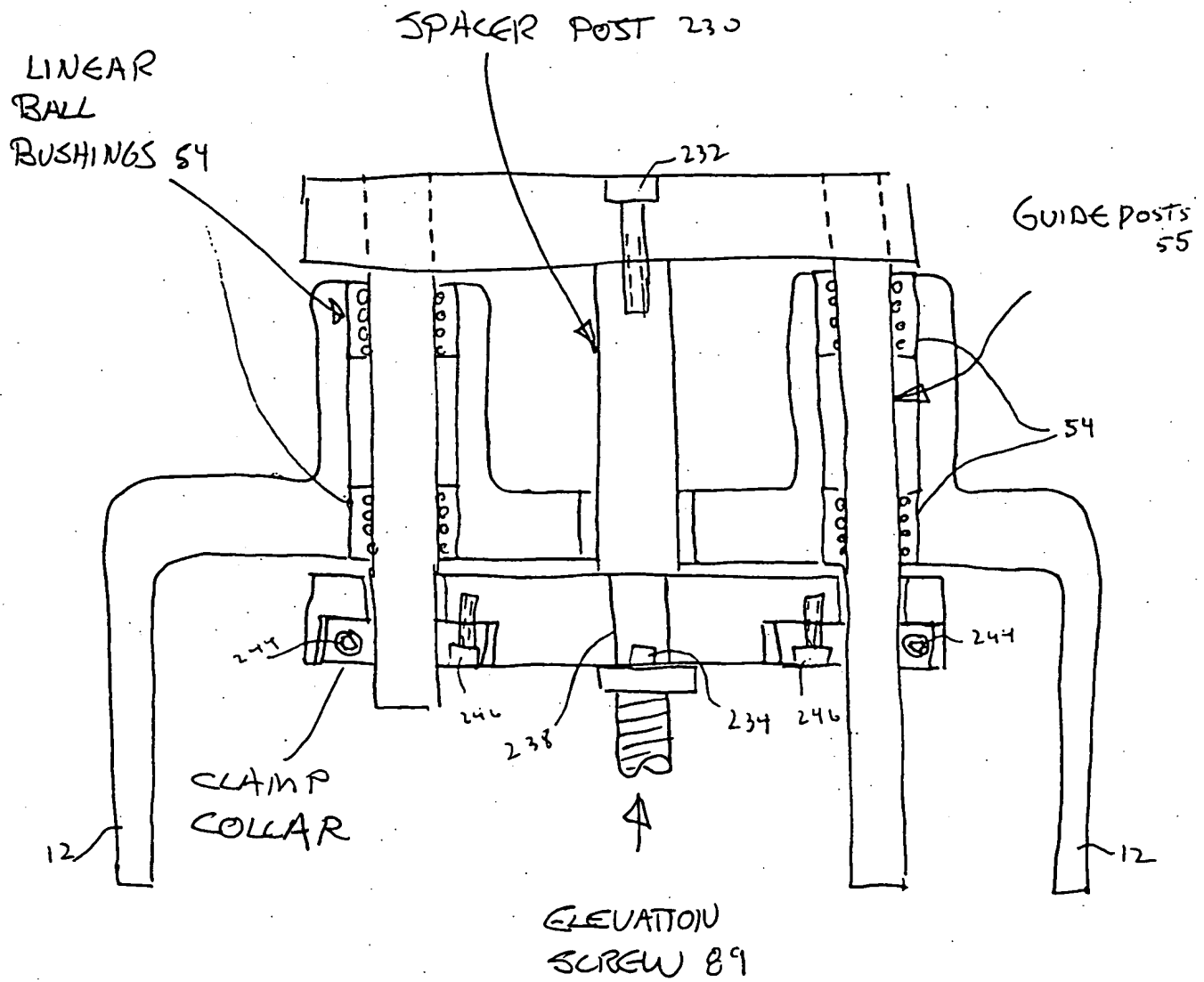
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FIG. 9A



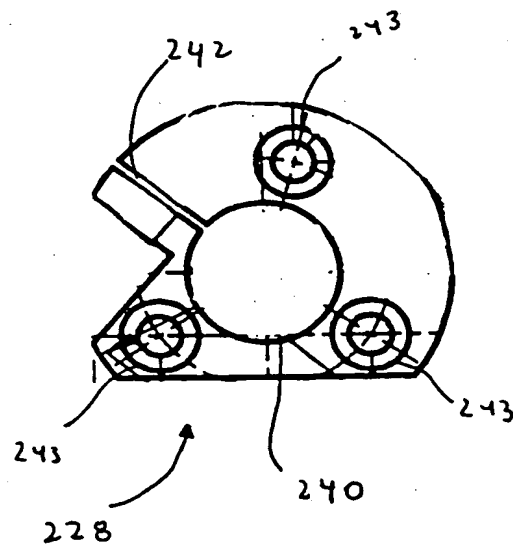
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FIG. 9B



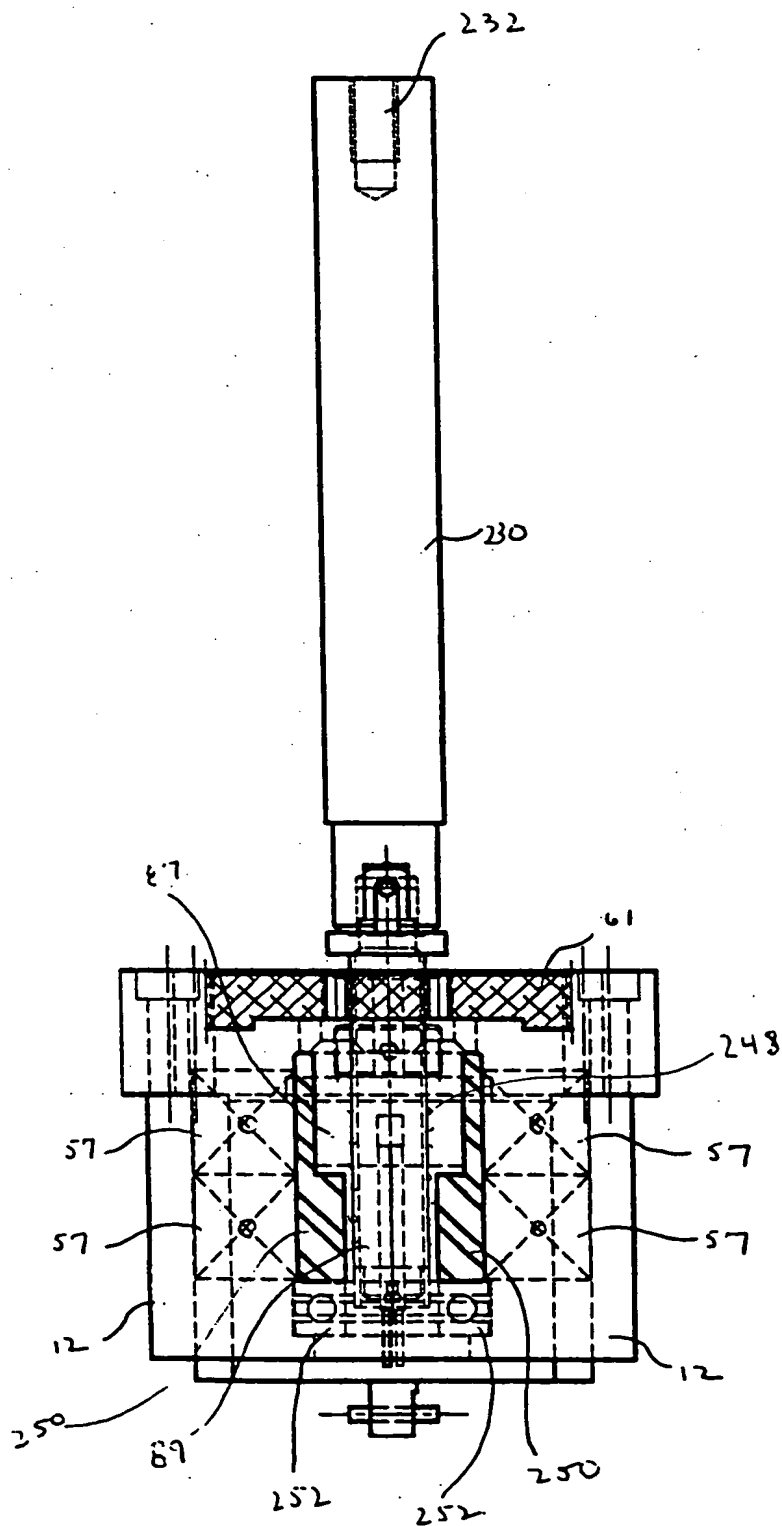
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FIG. 9C



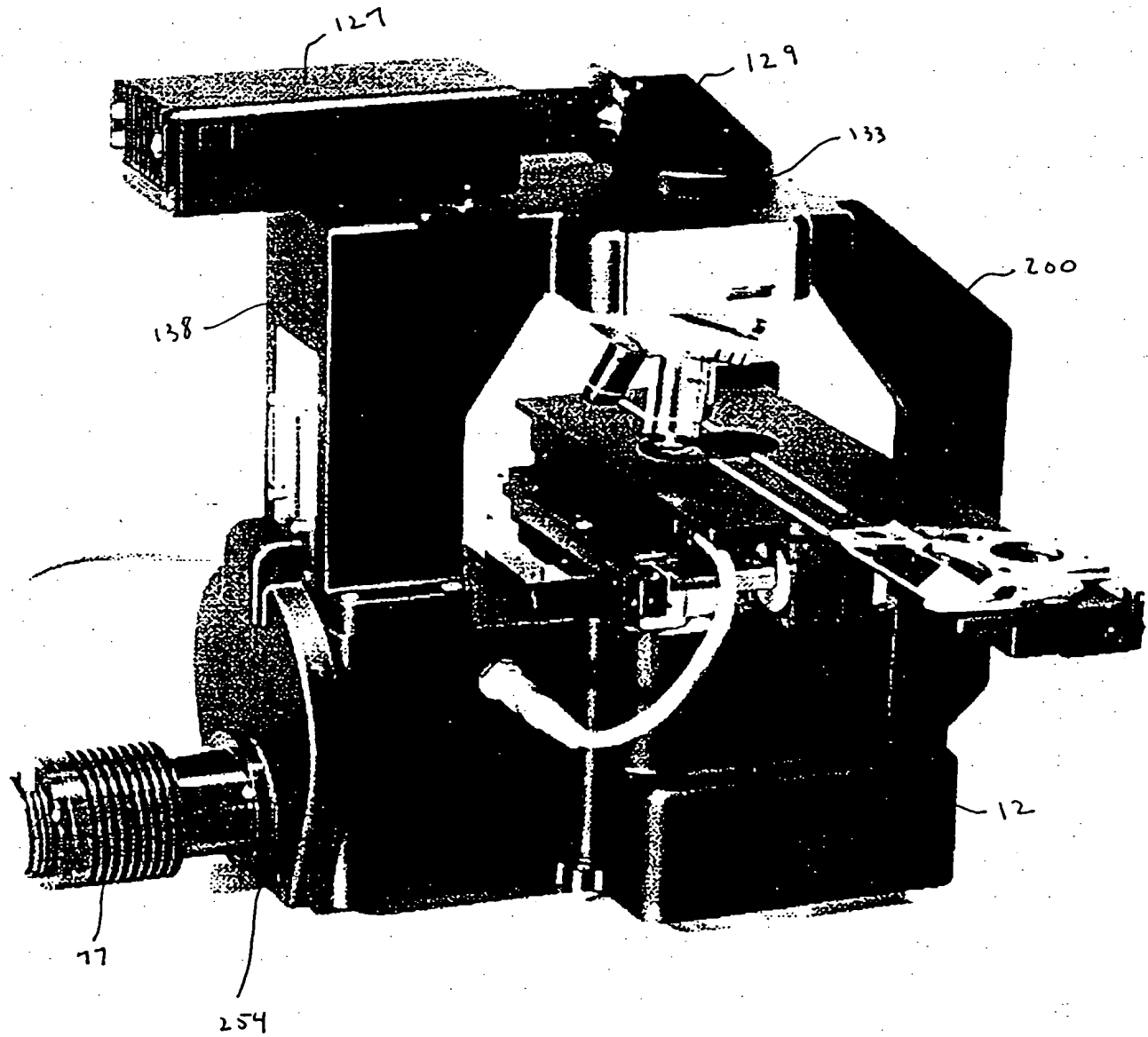
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FIG. 10



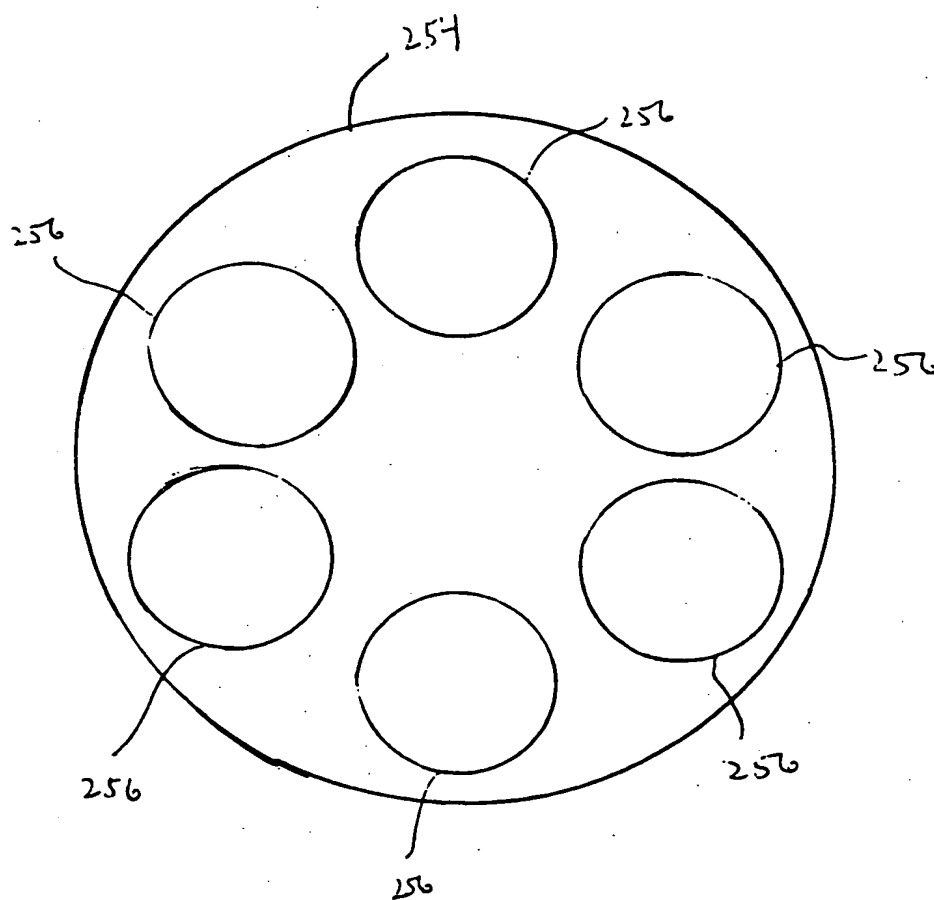
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FIG. 11A



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FIG. 11B



DETAILED DESCRIPTION OF A PREFERRED EMBODIMENT

Referring to Figures 1-6, there is shown a schematic block diagram of a system that incorporates the principles of the invention. In particular, the Figures illustrate a system having the capability to capture images of a sample from a specimen collected from an individual and placed upon a slide, and to analyze the sample rapidly, accurately, and precisely. The microscope system may be incorporated into a variety of settings and a variety of applications.

Exemplary Applications for Microscope System

Referring to Figure 1A, there is shown one example of a suitable configuration employing a microscope system according to the present invention. An automated video microscope having image analysis capabilities is coupled to a Data Management System (DMS). In one embodiment of the invention, the DMS comprises a conventional computer system with a processor and memory that contains patient medical history and demographic data relevant to the specimens being screened. The DMS preferably takes the form of a programmed general purpose desktop IBM-PC compatible computer which has sufficient storage and processing capability to run the Microsoft Windows operating environment and the Microsoft Visual Basic and Microsoft Access application programs. The DMS and the image analyzer are preferably coupled via a high-speed serial data link. The DMS may also be coupled to other data processing equipment via various types of local or wide area networks. In alternative embodiments, other data computing equipment may be used as would be known to persons of ordinary skill in the art. As shown in Figure 1A, a slide magazine 18, a bar code scanner 21 and display 17 may be used in combination with the microscope.

Referring to Figure 1B, there is shown a second application of the microscope. Automated sample analysis system 23 includes a microscope with fixed optics, described subsequently, and a computer system. Samples are input via a slide magazine feeder 19 and analyzed with the computer in combination with the microscope. The data from the analysis is sent via a cable 24 to an operator-based sample analysis system 25, which also includes a microscope. The operator-based sample analysis system 25 receives the data from the automated sample analysis system 23, and, with the assistance of the data, facilitates presentation of areas of the sample to the operator for analysis.